UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF NEW JERSEY

SUSAN HAINES, as Administratrix ad Prosequendum and Executrix of the Estate of Peter F. Rossi, Plaintiff	Honorable H.Lee Sarokin
VS.	Civil Action No.84-678(SA)
LIGGETT GROUP, INC., a Delaware corporation, LOEW's THEATRES, INC., a New York corporation, R.J. REYNOLDS TOBACCO COMPANY, a New Jersey corporation, PHILIP MORRIS, INC., a Virginia corporation, the TOBACCO INSTITUTE, Defendants	

Continued deposition of DR. DARRYL CARTER taken on behalf of the Defendant, R.J. Reynolds Tobacco Company, in the above-entitled cause before Kathleen M. Sweeney, Registered Professional Reporter, Notary Public in and for the State of Connecticut, on August 22, 1991 at 10:00 o'clock a.m. at the Marriott Residence Inn, Three Long Wharf Drive, New Haven, Connecticut pursuant to Notice.

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DR. DARRYL CARTER,

having been previously duly sworn, was further examined and testified as follows:

CONTINUED DIRECT EXAMINATION

BY MR. YOUNG:

Q We are back on the record. Doctor, I will once again hand to you another check payable to the order of Darryl Carter, M.D., in the amount of Two Thousand Four Hundred Dollars.

A Thank you.

Q And Doctor, I will remind you that you are still sworn and as I said yesterday, if I ask you questions that don't make sense to you or you just don't understand what I'm asking, then please note that to me and I will try to rephrase them, all right?

A Okay.

Q Similarly, if I ask you a question that you don't know the answer to, don't attempt to guess. Just let me know that you just don't know the answer, all right?

A Yes.

Q And I'm going to assume once again your answers are based upon your personal knowledge or your professional opinion to a reasonable degree of medical probability.

A Yes.

Q And finally, as I said yesterday, if I ask you a question that can reasonably be answered with a "yes" or "no", I would appreciate it if you would do that.

A Okay.

Q Now, yesterday, we talked briefly about your diagnosis, we talked extensively about your diagnosis of poorly differentiated adenocarcinoma for Mr. Rossi?

A Yes.

Q And I think you said, I would like you to correct me if I'm wrong, that that diagnosis is a diagnosis which is applicable under the criteria established by the Armed Forces Institute of Pathology and the World Health Organization, is that correct?

A Basically they're the same. When Dr. Eggleston and I wrote the fascicle, the people that, editorial board of the fascicle put us in touch with and has us meet with the WHO group to make sure that there was no serious disagreement between what we wrote in the fascicle and what the WHO was about to come out with as the second version of the classifications of lung cancers. So, they're not different. They're essentially the same. And it's not by accident, it's by design.

Q Okay. And if you were asked to classify Mr. Rossi's tumor under the AFIP it would be poorly differentiated adenocarcinoma, right?

A Yes.

Q If you were asked to classify it using strictly the WHO criteria it would still be poorly differentiated adenocarcinoma?

A Yes.

Q You indicated yesterday that you knew Dr. Daut, the prosector, right?

A Yes.

Q Have you ever discussed the Peter Rossi situation with Dr. Daut?

A No.

Q You also said yesterday that one of the animal studies that you relied upon in support of your causation opinion was Dr. Auerbach's Smoking Dogs Study, is that right?

A Yes.

Q I think you also said that you had even had an opportunity to see some of the slides from that case, is that right?

A Yes.

Q And so I wanted to ask you a question that I did not ask yesterday and that is, did you have any

personal involvement such as that, where you looked at the slides, in any of the other animal studies that you mentioned yesterday as those which you were relying on in support of your causation theory?

A No.

Q Now, Doctor, you would agree that it is important in any area of science for people to know the limits of that area, do you agree with that?

A Of course.

Q And would you also agree that people who devote their life to study in a science are probably in the best position to understand the limits of their science?

A I'm not sure I would agree as readily to that statement. Sometimes the people need to generate ideas and have them tested by a group of people and tested over a period of time before all of us can be certain that those ideas are true or not true.

Q Okay. Would you agree that the people who devote their life are at least in the best position to understand the limits of their science?

A I would agree they're in a good position. I'm not sure I would agree "best".

Q All right. Are you familiar with Richard Daul?

A Yes.

Q Epidemiologist?

A Yes.

Q Noted epidemiologist?

A Yes.

Q Let me read to you a statement from Richard Daul and I'm going to ask you if you agree with it. This is from a text edited by L.J. Whits Oxford University Press in London 1964 called Medical Surveys and Clinical Trials, and Mr. Daul's chapter is called "Retrospective and Prospective Studies". Here.

MS. WALTERS: Do you have a copy of that, extra copy of that?

MR. YOUNG: No.

Q Here is the statement I would like to know whether or not you would agree with this.

MS. WALTERS: What page is that on?

MR. YOUNG: Page 90.

Q "The results obtained in the prospective studies on smoking appear to be quite clear and it is certainly much easier to assess their significance than it was to assess the significance of the earlier retrospective studies. They do not, however, prove that smoking was the cause of the disease."

Do you agree with that statement?

MS. WALTERS: Can you let the witness look at the statement in context?

Q Do you need to look at it?

A I would like to.

Q Okay, sure.

A I think that within the context of what Daul is saying, that his statement is accurate.

MS. WALTERS: I would like to keep that out. I would like to have that marked as an exhibit at the end.

Q Let me read to you a statement from the 1964 Surgeon General's Report and I ask you if you agree with this.

MS. WALTERS: What page are you reading from?

MR. YOUNG: I'm not reading yet, Cindy.

Q Okay. I'm going to read you from Page 21. I'm going to ask you if you agree or disagree with this statement. "Although various disciplines and fields of scientific knowledge were represented among the membership, all members shared a common conception of the multiple etiology of biological processes. No member was so naive as to insist upon monoetiology and pathological processes where in vital phenomenom."

A I'm sorry I missed that. Pathological

processes were what?

Q "All members shared a common conception of the multiple etiology of biological processes. No member was so naive as to insist upon monoetiology in pathological processes or in vital phenomenom. All were thoroughly aware of fact there are series of events and occurences and developments in these fields and that the end results are the net effect of many actions and counteractions."

Did you understand that?

A Yes.

Q Okay. Do you agree or disagree?

A It's a pretty general statement. I think it's almost an axiom. It would be hard to disagree with the statement out of context. If we try to apply it in context, I think then we could either agree or disagree as to how to apply it.

Q So the answer to my question is "yes", you agree?

MS. WALTERS: The answer is what the answer is.

A The answer is a qualified "yes". I think it's such a general statement that it would be hard to argue with in general.

Q Okay. And so you don't argue with it in

general, is that right?

A In general.

Q So you agree with the?

MS. WALTERS: His answer. I'll object. His answer is what it is and attempting to browbeat him into something else is not proper.

MR. YOUNG: I'm not attempting to browbeat him.

MS.WALTERS: Yes, you are. I'll instruct the witness again, as I did yesterday, just because you're asked a question three times you are not required to change your response.

THE WITNESS: I understand.

MR. YOUNG: Okay.

A It is that it's such a general statement that it's like motherhood and apple pie, if you will, everybody is for it. There may be some circumstances where a general statement of that nature could be applied or it might not apply and I would be glad to discuss the situations where I think it does and where I think it does not apply.

Q But I haven't asked you to discuss those situations, have I?

A All right. My answer then would be that as a

general statement I think it is true.

Q Thank you. Let me read to you another statement from the Surgeon General's Report of 1964. And once again, I will ask you if you agree or disagree with it. "It is recognized that no simple cause and effect relationship is likely to exist between a complex product like tobacco smoke and a specific disease in the variable human organism."

MS. WALTERS: What page is that on?

MR. YOUNG: 31.

A I'm sorry. Would you reread it for me, please?

Q Yes. "It is recognized that no simple cause and effect relationship is likely to exist between a complex product like tobacco smoke and a specific disease in the variable human organism."

MS. WALTERS: Would you let the witness read that in context.

MR. YOUNG: He hasn't asked me.

Q Do you find it necessary to read this?

A No, I think I understand.

MR. YOUNG: He said he didn't need to.

MS. WALTERS: I heard him.

A I would disagree with it.

Q You disagree with it?

A Yes.

Q On what basis do you disagree?

A I think that tobacco smoke is a complex product. If one were, it contains a number of chemicals, compounds, which have been listed as carcinogens. I think if one were to say which of those compounds might be a causative agent, I think that one would be in trouble. I think that if one were to try to dissect out the dose response rate of each one of them it would be a very difficult proposition. But I think that to say that given forty different carcinogens which have been identified in cigarette smoke, to say that, you can't identify a causal relationship between any of them in a disease process such as lung cancer which arises in an area exposed to those compounds, seems to me to go beyond the proposal of reasonable medical certainty to absolute crystal clear certain knowledge which I think we agreed not to try to use as our standard.

Q This says there's no simple cause and effect relationship. Now are you saying you think there is a simple cause and effect relationship?

A I think I wouldn't know how they were defining "simple".

Q Well, how do you define "simple"?

A I would say that simple would be -- simple would be one that didn't require a great deal of thought or effort or work to demonstrate.

Q Okay. And based upon your definition do you think there is a simple cause and effect relationship?

A No.

Q Okay.

(Exhibit 13 marked for identification.)

Q Doctor, let me hand you what has been marked as Carter Exhibit 13, "Excerpt from the Office of Science and Technology Chemical Carcinogen Review Statement." Take a look at that, please. And specifically I would like to call your attention to Page 10379, the section that says "Current Beliefs". Do you see that? That's in the chapter one called "Current Views on the Mechanism of Carcinogens" and subparagraph or subsection C, "Current Beliefs".

What I propose to do is to read each of the eight paragraphs and ask you if you agree or disagree. Tell me when you're ready to have me do that?

MS. WALTERS: Do you have an extra copy of this?

MR. YOUNG: Didn't you give her one, Paul?

Q Have you had a chance to look at that?

A I just want to see the publication.

Q Okay. The paragraph, first paragraph says, "First, answer can be induced by radiation biological physical and/or chemical agents."

Do you agree or disagree with that statement?

A I agree.

Q Then it goes on, "Second, on a biochemical and molecular level there are important similarities among the million species."

Do you agree or disagree?

A I agree. As far as the statement goes.

Q I didn't ask you any anything else, did I?

A No, you didn't.

Q The third paragraph is, "Third, an estimate of the potentcy of carcinogens may never be exact and may vary with lifestyle, habits, age, sex, individual genetic differences, ethnic background, test strains and/or species, diet, dose rate, routs of administration, vehicle or solvent used, if any, as well as the presence or absence of other agents in the environmental condition prior to, during or after exposure."

Do you agree with that?

A I think it's an incomplete statement.

Q Does that mean you don't agree with it then

as it's stated?

A I think it's an incomplete statement.

Q Okay. Let me go to the next paragraph. "Fourth, cancer development is a multi-stage process that may involve the geno, both indirectly, frequently termed epigenetic events and directly which may include the participation of chemicals or viruses and which may be modulated by higher order functions, i.e., at the organ and organismic level."

Do you agree or disagree with that?

A In general I agree with it. I'm not familiar with the term "organismic".

Q The next paragraph, "Fifth, numerous factors may alter the frequency of cancer induction by altering one or more of these stages."

Do you agree with that?

A Yes, I agree with that.

Q "Sixth, the genesis of a cancer appears to require an alteration in the ability of a cell to elaborate its appropriate genetic program, i.e., in its information processing capacity with a subsequent fixation and propogation of that alteration."

Do you agree with that?

A No.

Q Okay. The next paragraph, "Seventh, we still

lack an in depth understanding of the mechanisms and stages of cancer induction and expression."

Do you agree with that?

A Yes.

Q "Eighth, only by understanding the stages of tumorogenesis and carcinogenesis, the substances and processes which modulate them and how these may differ among cells, organs, individual strains and species will we ultimately understand the role of substances, radiations, viruses and/or life style factors in human cancer."

Do you agree with that?

A Yes.

Q Thank you. Do you agree that we do not know how many stages are actually involved in the development of adenocarcinoma of the lung?

A No.

Q Okay. How many stages are there?

A There are at least several which could be defined in a number of ways.

Q But can you put a number on those stages?

A I think they might be variously defined by different people and stages might be subdivided to give a number that might seem to come out in a different way.

Q Do you have an opinion as to how many stages there are?

A I have an opinion as to the stages.

Q Okay. And how many are there?

A The stages would include first of all the induction of the carcinoma.

Q The induction of the what?

A Carcinoma.

Q Okay.

A The second stage would be a variety of alterations which would, in general, enhance the induction process. Thirdly, there would be a growth stage and, finally, there would be a stage which would allow the, in which the tumor cells acquire the ability to spread beyond the area in which they started. And finally there would be a stage in which the tumor cells acquired the ability to grow in another site.

Q Now, when you said the first site, the first stage is induction, were you talking about induction at the one cell level?

A One or few.

Q And in talking about the enhancement level are we still talking about one or few?

A The individual cells might have propagated to a somewhat larger number at that point.

Q And what about the growth stage? Does that involve a propagated tumor?

A That entails the multiplication of the number of tumor cells.

Q And how does that differ from the spread stage?

A The ability to grow would be comparable to the expansion of a group of cells to form a single larger mass which is not the same as the ability to spread through normal tissues.

Q And then the spread stage does involve the spread through the normal tissues, is that right?

A Yes.

Q At what stage do you have what you would diagnose as cancer?

A I'm sorry.

Q What stage would you diagnose a cancer, would you call it actually a cancer? Would that be the induction stage?

A I would guess that it would become a cancer at the stage in which it has undergone growth to the point where it becomes visable, either grossly and/or microscopically. If it were grossly visible it would be microscopically visible. It might be microscopically visible without being grossly visible.

Q Now, you said you would guess. Does that mean something less than an opinion that we talked about?

A No, it's my opinion that it would be diagnosed at that stage.

Q Fine. Do you agree that science knows why one cell turns malignant when another cell that's exposed to the same exposure does not?

A There are have inferences. I would say that with a reasonable medical certainty that there are certainly major gaps in our knowledge at this time.

Q Okay. Would you agree that science doesn't know why one animal exposed to the same exposure as another animal can get cancer and the other does not?

A Yes.

Q Okay.

Q Do you agree that most lifetime smokers never get lung cancer?

A Yes.

Q And do you agree that some people who never smoke can get lung cancer?

A Yes.

Q And do you agree that people can get lung cancer for reasons other than cigarette smoke?

A Yes.

Q And maybe more specific, do you agree that people can get adenocarcinoma of the lungs for reasons other than cigarette smoke?

A I'm not certain of that.

Q But you believe it to be the case?

A It may be true.

Q Do you have a reasonable, an opinion to reasonable medical probability on that point?

A I think it is possible for a non-smoker to develop adenocarcinoma, unlikely.

Q Can you frame that in terms of reasonable medical probability?

A I'm not sure of the nature of your question. Are you asking me, is it likely that a non-smoker could develop an adenocarcinoma.

Q In your opinion to a reasonable medical probability people can get adenocarcinoma of the lung for reasons other than cigarette smoking?

A It is possible.

Q Can you answer that question"yes" or "no"?

A Yes, it is possible.

Q All right. Would you agree that smokers could get adenocarcinoma of the lung for reasons other than cigarette smoking?

MS. WALTERS: Are you asking him to

exclude cigrette smoking as any factor in it or --

MR. YOUNG: No.

Q Did you understand my question?

A Yes, I did.

Q Can you answer my question?

A I'm trying to sort through your question.

Q That's fine.

A So I can reply accurately to it.

Q I don't want to rush you?

A I would say medically we would be unable to make that determination, so from a medical, reasonable medical certainty I would have to say that the answer to that would be "no".

Q When did you first reach your opinions about smoking causing disease?

A I can't give you a date. I would say that was in the latter part of the 1960's.

Q Was this after you got out of medical school?

A Yes.

Q Was smoking and disease a subject discussed in medical school when you were a student?

A It was not discussed very actively when I was in medical school.

Q Do you remember any discussions on the

subject?

A I can't recall specific discussion on the subject.

Q Do you recall a consensus among the faculty?

A I recall that during medical grand rounds that after the last patient was presented that virtually everybody in the audience lit up either a cigarette or cigar.

Q So you think your opinions were formed sometime in the late 1960's?

A Yes.

Q And do you remember what it was that led you to make that conclusion at that time?

A I think it was a combination of events, one being are the Surgeon General's Report which had gotten some publicity. The second thing was that I became involved in the project that I mentioned yesterday, the screening for early lung cancer and I started to actively address the literature on the subject.

Q And did your opinion with respect to adenocarcinoma and cigarette smoking as well as poorly differentiated adenocarcinoma and cigarette smoking, also become formed at approximately that same point in time?

A I think that it was my impression in the

early '60's that the cancers that were most likely to be associated with cigarette smoking were those listed by the Kryberg criteria and those were the squamous cell and possibly the small cell carcinoma, but the information that I have read subsequently has indicated that that was not correct and, therefore, have subsequently thought that there's reasonable medical certainty to suggest that adenocarcinoma is as significant, as significantly related to cigarette smoking as are the other types of lung cancer.

Q Can you approximate the timeframe that you came to that conclusion?

A That was probably through the 1970's that I came to that conclusion.

Q Sometime in the 1970's?

A Yes.

Q Let me switch gears from cigarette smoking and disease and talk about the concept of lung scarring and cigarette smoking. Do you believe that cigarette smoking can cause non-malignant lung scar?

A Yes.

Q And what is the basis for that opinion?

A The basis for that is the fibrosis that's an important part of pulmonary emphysema which has been tied with a high degree of medical certainty to

cigarette smoking in most cases.

Q And do you believe that cigarette smoking can cause lung scarring in any other manner other than through emphysema?

A It can be associated within interstitial fibrosis which is not fully characterizeable as pulmonary emphysema.

Q Anything else?

A I think it's clear that cigarette smoking may increase the likelihood and therefore increase the -- or lead to the development of infections within the lung which may subsequently wind up as fibrosis, either localized or interstitial.

Q Such as what, bronchitis?

A Such as severe bronchitis going onto bronchiectasis which would lead to pneumonia distal to the abnormally functioning bronchi.

Q So let me see if I understand it. You believe that cigarette smoking can lead to bronchitus and pneumonia, is that correct?

A Yes.

Q And you believe that bronchitus and pneumonia can cause scarring?

A Bronchitus, severe bronchitis and pneumonia, some forms of pneumonia may go on to scar.

Q You would also agree, though, that people can contract severe bronchitus for reasons other than smoking, wouldn't you?

A Yes.

Q And that in itself could lead to scarring, couldn't it?

A Yes.

Q And people can contract severe forms of pneumonia for reasons other than smoking, is that right?

A That is correct.

Q And that severe pneumonia can in fact lead to lung scarring, is that correct?

A Yes.

Q And indeed there are several others diseases that can cause lung scarring other than through cigarette smoking, isn't that right?

A Yes.

Q For example, we touched on TB yesterday, is that right?

A Tuberculosis can lead to scarring.

Q Sure and histoplasmosis, things like that?

A Histoplasmosis may lead to scarring.

Q Pulmonary infarct can lead to scarring?

A Yes, it can.

Q Trauma can lead to scarring, can't it?

A Yes.

Q Now, yesterday we talked about your feeling that lung tumors can themselves cause a fibrotic reaction, do you remember that?

A Yes.

Q Desmoplastic reaction, or a scar, is that right?

A Yes.

Q Do you have a theory as to the mechanisms by which those lung neoplasms can cause scarring or the desmoplastic reaction?

A Yes.

Q Would you tell us that theory?

A The theory that seems to be most plausible is that the tumor cells may elaborate products which cause normal cells to lay down collagen, to normal cells to both come to the area in which the tumor cells are present and subsequently to lay down collagen.

Q And do you know how it causes that or why it causes those cells to lay down collagen?

A The growth factors elaborated by the tumor would cause the normal cells to function as fibroblasts and their function is to lay down collagen. A second, or perhaps a corollary of that idea is that the tumor

cells injured the normal tissue in such a way that the normal tissue elaborates the growth factors which lead to fibroblasts to form collagen. I think that either or most likely both of those mechanisms may be operating.

Q That's your opinion to reasonable medical probability?

A Yes.

Q Now, we discussed yesterday the concept of the old scar cancer, do you remember that?

A Yes.

Q And typically that was associated with a peripheral tumor, isn't that right?

A Yes.

Q And it was typically associated with adenocarcinoma?

A Apparently.

Q Although it had been associated in some cases with squamous cell carcinoma?

A And with small cell.

Q And with small cell?

A And I would presume with large cell carcinoma as well.

Q I believe you testified yesterday, too, you thought in some rare cases preexisting scars can, in

fact, form tumors, is that right, or cause tumors?

A I think that they may be the site at which tumors develop. Whether or not they cause it, I think is not quite the same thing. They may be the nidus upon which the malignant cells develop, but I don't think that the formation of the collagen leads to malignant change in the cells around it.

Q But do you think there is a cause and effect relationship between the preexisting scar and the tumor that subsequently develops?

A Would you repeat that for me?

MR. YOUNG: Would you read that?

(The pending question was read.)

A No.

Q So, is it your opinion then that the fact that you can find some tumors at the site of pre-existing scars is a happenstance situation?

A I think it may be more than happenstance, but that is not to say that the scar, itself, the collagen that's there causes the cancer. I would say that it's highly unlikely that that occurs and, furthermore, I can't think of any hypothesis to suggest how that might occur.

Q Can you explain then the basis for your statement that you think it may be more than

happenstance?

A I think that there are two ways in which that might occur. One is that the injury which produced the scar also acted as a carcinogen. That's not the same thing as the scar causing cancer. The second possibility is that the scar altered the local situation in such a way that the cells behaved or proliferated in the vicinity. And the third possibility, of course, which I think is the most likely, is that the tumor cells themselves in some way have caused the scar to develop as the tumor grows.

Q I understand that that's your opinion. I'm trying to focus on the situation where a tumor develops at the site of a preexisting scar. And you said that you thought there were two theories as to how that could occur, is that right?

A There are two ideas. The first being that the agent responsible for the injury that produces the scar is also a carcinogen. And there are many examples in the literature to indicate that the first recognizeable pattern of response to a carcinogen is the same or appears to be the same as an injury pattern. So that that is one possibility.

The second possibility is that there is a proliferation of the cells at the, associated with the

injury which results in the scar.

Q And do you have an opinion to a reasonable medical probability?

MS. WALTERS: Were you finished with that last part?

A No, I wasn't.

Q Go ahead.

A Well, could you read where I got to.

(The answer was read.)

A And that the proliferation of those cells is the second part of the process of carcinogenesis. That is the enhancement or the propogation of induced cells.

Q Okay. Let me ask the question I started to ask earlier. Do you have an opinion to a reasonable medical probability as to those theories, being the theories that are applicable to explain how tumors can arise at the site of a preexisting scar?

A Are you asking which of those two that I --

Q Yes, I'm asking whether you subscribe to one or both of those theories or neither?

A I think that either of them is possible. I would guess that it is more likely that the second one that I talked about is more likely than is the first.

Q Okay. And is that then the theory that you would subscribe to to a reasonable medical probability?

A Yes.

Q And can you explain that theory in a little more detail to me?

A What I would reiterate is that if a scar, if an injury occurs which results in a scar, that during the process by which the scar is forming there is a proliferation of cells in the vicinity of the area in which the scar is proliferating. If under normal circumstances the cells that are proliferating have not been induced to become malignant cells, then when the stimulus driving the response, the injury response, ceases, then those cells would cease to proliferate and return to normal.

If, on the other hand, the cells had been genetically altered, then the proliferation of those cells might be the second phase of the process of carcinogenesis and lead to a fully developed -- subsequent to the growth of those cells then it would lead to the recognition of the process as a cancer.

Q Are you familiar with the Spencer-Raeburn theory on the continuation of regenerating hyperplasia?

A Yes.

Q And is that the theory you just expressed?

A I think that's not precisely the opinion that I expressed.

Q How does it differ from their theory?

A I think it suggests that there is something in the area which leads to a continuous proliferation of the cells, and I'm not sure I understand that part of their idea.

Q It's your theory or it's their theory that there is something in the areas that leads to a continuation of the regenerating cells?

A As I understand their idea, which was formulated a while ago and can't be easily translated into the sorts of ideas expressed there in the Federal Register, for example, their idea is that there is some continuing injury which would lead to continuing proliferation. I think that that's not entirely consistent with the idea of a mature scar. In that a mature scar would be a, the end product of an inflammatory process. What they are suggesting is that there is some continuing stimulus to proliferation and that has to be separate from the scarring. So I'm not sure that they are entirely consistent in their view on the scar cancer.

Q And are you suggesting that there is a, that there is something in the environment that stiumulates the cells that are proliferating to go beyond into a malignancy?

A I think that simple proliferation does not lead to malignancy. There must be, as mentioned in the Federal Register there, there must be an injury by an agent which leads to a genetic abnormality, that that single hit, or minimal hit, if it's one cell or a few cells, can't result in cancer by itself unless it is multiplied by the process of the proliferation of the cells. And what I believe Raeburn and Spencer were suggesting, or partially suggesting, or alluding to, or getting at, or trying to explain, is that the proliferation of cells is what may occur at the site of injury which results in a scar, but that the proliferation of cells alone would not lead to a malignant tumor. There must be some other process, be it a chemical carcinogen or some other type of carcinogen, which alters the cell first so that the subsequent proliferation of the cell can lead to the full development of a malignancy.

Q And that "some other process" could be anything that could cause cells to become malignant, is that right?

A That would be one of the agents that alters the genetic constitution of the cell, which is more or less the definition of a carcinogen, which would include all of the agents that would be listed as

carcinogens.

Q And that would include, for example, to take yesterday's example, high levels of radiation?

A Yes.

Q Do you agree that scars, that malignant growths can arise at the site of scarring in organs other than the lung?

A Yes.

Q And do you believe that the process involved in that malignant growth would be essentially the same as the process that you just described for the lung?

A Yes.

Q Are you aware that malignant growth, for example, has been seen at the site of certain skin scars?

A Yes.

Q Now, why don't you state for me your opinion regarding the relationship between the tumor you saw in Mr. Rossi's lung slides and the scarring that you saw in the lung slides?

MS. WALTERS: I thought he did that yesterday.

MR. YOUNG: I just want him to make it clear for the record.

MS. WALTERS: Do you want him to now

retestify about what he testified about yesterday, or do you want to know if there's something he can add to that?

Q Well, it's my understanding, but I'm not clear that the record is clear, that you believe that scarring is a desmoplastic reaction, is that right?

A Yes.

Q Okay. And the reason that you think that it is a desmoplastic reaction is because you see a desmoplastic reaction not only on some lung slides, but on some slides from metastatic sites, is that correct?

A Yes.

Q But looking at the lung slides alone, you can't distinguish desmoplastic reaction from preexisting scar without conducting one of the more sophisticated tests we discussed yesterday, is that right?

A If you limit it to looking at the slides of the lung, then it would not be possible to distinguish the age of the scar.

Q And those more sophisticated tests, I think, were, what, immunofluorescent staining, is that right?

A Yes.

Q What was the other one?

A Either immuno or immunohistochemical which

are just different methods of showing the same thing.

Q And you never ran any of those tests on the Rossi pathology, did you?

A No, I did not.

Q And to your knowledge no one ever has, is that correct?

A That is correct.

Q In support of your desmoplastic reaction theory, you would rely on your own studies that you and Dr. Madri conducted for one thing, is that right?

A That would be one thing.

Q And we mentioned Dr. Shimosato's study?

A Yes.

Q What else do you rely on?

A There are, I believe, some three studies which have subsequently been carried out that confirm the findings that Dr. Madri and I reported.

Q Do you know the names of those studies or do you remember the authors?

A I can refer to them, if you --

Q Yes, please. Do you have a reference with you?

A I have a book called Lung Cancer: The Evolution and Concepts.

Q Can you list the authors so she can get it

into the record. That's your book and I assume we can't keep it, for the record?

A I would like to keep it.

Q Yes, so if you could just identify it so we can --

A The editors are Gruhn, G-r-u-h-n and Rosen, R-o-s-e-n, it was published by Field and Wood, Copyright 1989 and the city is New York. Publication of this book, interestingly enough, was sponsored by the Tobacco Council.

Q Do you have any research grants from the Tobacco Council?

A No, I don't. On Page 87 and going over to Page 91, there is a discussion of the scar cancer idea. They discuss our publication and then they discuss a publication by El-Torky, et al, which seem to confirm that.

Q Are you familiar with that publication El-Torky?

A I can give you the reference.

Q But have you read it?

A Yes. The other material that I can give you, and I don't have this with me, is the latest edition of the Robbins textbook of pathology which mentions this study.

Q This study is El-Torky?

A Our study, Madri and Carter, and also a study by Barsky, et al which also confirms.

Q Are you familiar with the Barksy Study, too?

A Yes.

Q So there's four studies, yours with Dr. Madri, Dr. Shomosato's, the El-Torky and the Barsky?

A There are other studies which deal with clinical material. In attempting to assess the relationship of the scar to the tumor, in clinical material. They did not take a direct look at the types of collagen and, in fact, Shimosato did not evaluate the types of collagen.

Q Do you recall the names of any of the clinical studies?

A One of them is the article that I cited for you yesterday, that article by Cuhn, et al.

Q Kuhn, et al?

A I think it's Kuhn or Kaun.

Q K-u-h-n?

A It was in that Annual Review of Respiratory Disease, and I think the reference is in there, saying that the relationship appeared to be between tuberculosis and between infarct-like scars appear to be incidental, and then there are a couple of other

studies, perhaps two, and I don't have the direct references but I can get them in a very short period of time for you.

Q Do you have a general recollection on these other studies as to approximately the point in time they were published?

A They were all subsequent to the Shimosato article.

Q Do you think subsequent to yours, too?

A And the others were subsequent to the Madri-Carter article.

Q Okay. Let's discuss your article.

(Exhibits 14 and 15 marked for identification.)

Q Doctor, let me hand you what has been marked for identification purposes as Carter Exhibits 14 and 15. Can you take look at them and identify them if you can?

A What would you like me to do?

Q I'm trying to just get you to confirm that these are copies of your studies?

A Yes, they are.

Q What is 14?

A 14 is two pages of an excerpt from the Journal Laboratory Investigation Volume 46, pages, it's

1-a, and I presume it's 2-a. I don't see the page number on the second page.

Q Second page of the exhibit though, in any event, makes reference to some work of yours and Dr. Madri's, right?

A Yes. And there is on the second page or the next page there is an abstract entitled "Immunofluorescent Analysis of the Specific Types of Collagen Found in Association with Pulmonary Neoplasms", Joseph Madri and Darryl Carter.

Q And look at the next exhibit and identify that, if you would, please?

A The next exhibit is a copy of an article entitled "Scar Cancers of the Lung, Origin and Significance", same authors, and this is from Human Pathology, Volume 15, Pages 625 to 631, 1984.

Q And those are the two articles that you coauthored with Dr. Madri on scar cancer, is that right?

A It's basically the same article, first published in abstract form, and then subsequently, the full manuscript.

Q So it's the same project even though it's two different pieces of paper, is that right?

A Yes.

Q Why don't you just give us a description of what that project was, what was your hypothesis, what did you determine?

A Because of the Shimosato article which suggested that the scar seen in the scar cancer formed as a result of the growth of the cancer rather than prior to the growth of the cancer, I decided that it would be interesting to try to test the hypothesis with Dr. Madri who had developed antibodies to the different types of collagen and who had published an article prior to this with Dr. Furthmayer, that's reference 18 in the Human Pathology paper. I discussed the idea with Dr. Madri who felt that it was possible to distinguish, with the use of these antibodies, between scar which had recently formed and scar which was mature.

So we collected a group of cases sequentially. There were seven consecutive cases which fit the definition of scar cancer of the lung, that is, it was a carcinoma in the periphery of the lung that was associated with the scar. We collected these in the surgical pathology laboratory, and then Dr. Madri carried out a staining process with the antibodies to the various types of collagen and then exposed them to the fluorescent microscope and photographed the

lesions, seven consecutive lesions, and I believe we had some controls. What the results of that analysis were, the results of that analysis is Table 3 on Page 630 in which we say, "In establish pulmonary fibrosis Type 3 collagen was decreased", indicating a mature scar whereas in the scar cancers all seven of the scar cancers Type 3 collagen was increased indicating that it was an on-going process.

So, we felt that after having looked at these cases that one could only conclude that in seven consecutive cases representing no particular selection of cases, just those that came through the pathology laboratory, that it was likely that the, in these seven cases the scar was continuing to form as a result of the growth of the carcinoma, and that because we had seven consecutive cases in which we found this, that it was likely that that was the interpretation of most scar cancers. Obviously with only seven we couldn't say that the cancer could not be associated with a mature scar, but we thought that it was likely that in the majority of cases the hypothesis that we postulated would be fulfilled and that the tumor in one way or another was associated with the production of the scar, either directly or indirectly.

Q Dr. Madri was a colleague of yours at Yale at

the time?

A Yes.

Q Is he still at Yale?

A Yes.

Q Do you recall the timeframe that you did this work?

A It was, I would guess, in primarily 1982 that we carried this out. The publication was sent in to Human Pathology and you can see that they received the manuscript in May of 1983, but didn't publish it for over a year after that due to the fact that we, they asked us to make a minor revision which they accepted July 27, 1983 and then it took a year before they could schedule the article for publication.

Q So it appeared in 1982 as a probably point in time?

A 1982.

Q Let's look at the first one, the abstract. Now, as I understand it at that point in your study you had analyzed three pulmonary tumors, is that right?

A Two. It looks like an atypical pseudo lymphoma then a poorly differentiated carcinoma and a bronchiole carcinoma. And a typical pseudo lymphoma is not a malignant tumor.

Q Okay. So you had two malignant tumors at

that time, right?

A Yes.

Q And were those two malignant tumors then part of the seven that you referred to in the second paper?

A Yes.

Q And then let's look at the second paper. Did you subtype those tumors, in addition to, two of the seven are bronchiole carcinoma and a poorly differentiated, do you recall breaking down the other five?

A They were all adenocarcinomas. They had a bronchioloalveolar pattern, but they were not, obviously from the definition I gave you yesterday, they were not bronchioloalveolar carcinomas.

Q I'm just trying to find out, we went through this bit about one level it's either oat cells or not oat cells, then it's squamous or adeno, then the other level you can talk about the subtypes. I'm wondering if you did get into the subtypes on the other five, if you recall?

A I don't recall that I broke them down as to whether they were well, moderately or poorly differentiated.

Q Okay. Then as controls you used some non-malignant areas of fibrosis, is that right?

A Yes.

Q Do you remember whether they were taken from any particular part of the lung?

A No, I don't.

Q Do you recall whether you were able to determine the cause of any of those scars?

A We were not able to determine the cause of any of those scars.

Q Sometimes it's difficult to determine the cause of a mature scar as I understand, is that correct?

A I think once a scar becomes mature it's impossible to determine what it is that caused it. One has to look at other areas where the process is continuing to occur to infer what caused the particular scar that you are seeing.

Q So even in the case of a TB scar, if it's fully matured you can't identify it as a tubercular scar?

A That is correct.

Q Now, did you check on fibrosis in lymph node metastases here?

A No. These were all primary tumors in the lung.

Q I know that, I'm wondering in the addition to

the tumors you found in the lungs, did you check for metastasis elsewhere?

A Yes.

Q And what did you find? Where are you looking?

A I'm looking on Page 626 at the paragraph called "Histologic Findings".

Q Okay.

A "The degrees of fibrosis in the lymph nodes associated with metastic tumor vary considerably but not unpredictably. Lymph node metastases were present in twelve cases." Now, let me just stop for a moment here and explain why the number twelve appears there. In addition to the study with the seven cases, we also pulled out a group of sixty-nine resected periperal adenocarcinomas of the lung which we looked at with a light microscope alone. We did not look at those with the collagen type. And the statement with regard to the histologic findings in the lymph nodes regards to histologic findings only and not to immunofluorescent studies.

To continue on with that paragraph, "The degree of fibrosis in the lymph nodes was the same as or greater than the degree of fibrosis in the central portion of the primary tumor except in cases in which

only small deposits of carcinoma in the lymph nodes which were restricted to the peripheral sinuses were present. In all well established metastases, there was good correlation between the degree of fibrosis in the lymph node and that of the primary tumor. Data not shown."

Q Were these lymph nodes all in the thorax?

A They were all in the thorax, and, in general, they were associated with the lobectomy which was carried out for the treatment of these tumors.

Q Did you check in these cases for mestastasis outside the thorax?

A All the cases were clinically checked prior to the time of surgery for the presence of metastases outside the thorax. Had there been metastses outside the thorax, the patients would not have gone to thoracotomy for resection because they would have been incurable.

Q So unlike in Mr. Rossi's case we don't know, we don't have, for example, metastases to the spine or adrenal that we can compare for these specimens, is that right?

A That's correct.

Q And on that page it says you "found no major differences in survival according to the type or degree

of fibrosis present in the tumor", is that right?
A That is correct.
Q And no significant correlation of stage and scarring?
A That is correct.
Q Then down later on, on that page it says you "found increased levels of Types 1, 3 and 5 collagen and scars associated with tumor"?
A Yes.
Q And then going over to the next page it says you "found increased levels of Type 1 and 5 collagen and scars not associated with cancer"?
A Yes.
Q "And a decrease in Level 3"?
A Yes.
Q Or Type 3, I should say. And that's increased compared to what? I am a little confused here.
A That would be compared to normal.
Q Okay. So let's back up a second on the Page 626 where it says "there is an increased level of Types 1, 3 and 5 collagen with scars associated with tumor" that's an increase over normal, is that right?
A Yes.
Q Is that then different from an increase over

your controls?

A In the controls there was an increase in Type 1 and 5, but a decrease in Type 3.

Q Okay. And I'm a little confused when I read this. Is it an increase in the tumors compared to the controls, or is there an increase compared to something else, that's where I'm confused?

A There's an increase in Type 3 collagen in the tumors.

Q Yes?

A Compared to the controls.

Q Okay. All right.

A 1 and 5 are not useful. All they indicate is that they're present in either the mature scar or the on-going scar. They, of course, contribute to the bulk of the scar and may be very important for other reasons, but for the specific purpose of determining the age of the scar, they're not useful. It's only the Type 3 which is deposited early on and then apprently replaced as the scar matures.

Q Where I was confused is that if you read that full paragraph it says "there is an increase in Types 1 and 5", excluding 3, for a second, for the time being, in the tumors and in increase in 1 and 5 in the controls, and, therefore, you couldn't be comparing

them to each other for those types, is that right?

A Well, that's correct. You read it correctly. There is an increase in 1 and 5.

Q In both?

A Both.

Q Compared to what you would expect to see in a normal piece of parenchyma, I guess?

A That is correct.

Q But there is an increase in Type 3 in the tumors compared to the control?

A Yes.

Q Okay. Then, as I understand your reasoning, you interpret the increase in Type 3 as suggesting then an on-going response to the tumor, is that correct?

A An on-going formation of scar.

Q Right.

A Which could be interpreted in one of several ways. And then we discussed the reasons that we came to the conclusion that it was a result of the growth of the tumor rather than one of the other hypotheses presented.

Q Okay. And then let me call your attention to Page 630.

Q In that bottom paragraph on the left side it says, "The mechanism by which the scars form is not

apparent," is that right?

A Yes.

Q And is that still your belief?

A Well, that's a question of how certain one wants to be. At one level, does the scar form as a result of the presence of the cancer in some way or another. I think the answer to that is in these cases, yes, and we think most likely in most cases, yes. Now, as to the growth factor that's produced all the mechanisms involved in terms of being able to completely reproduce the situation, of course, we don't understand that. So, what I believe this says is that the mechanism, the full mechanism, the step by step process by which this occurs, is not apparent. But if you take as a major contrast to whether the scar precedes or follows the development of cancer, then I think the answer to that we do know.

Q You then go, on to describe a theory of Haupt and Kuhn and Gray and O'Neal?

A Yes.

Q By the way, is that the Kuhn article that you were referring to?

A No, it's not. The article that I referred to is, I believe, 1985.

Q Is that the same person, do you know?

A I think it's not. This is Kuhn with an umluat and the other article was from Hong Kong.

Q Are either of those articles, the Haupt and Kuhn and Gray and O'Neal, articles that you were relying on and the studies you couldn't recall?

A No, neither of those.

Q And you go on to say that they "suggested a mechanism in which scar formation is the result of repeated episodes of tumor necrosis and healing." Apparently your study didn't support that theory, is that right?

A That is correct.

Q Do you know whether the articles that you mentioned or any other articles have attempted to replicate your study?

A Not precisely. They have used different methods of looking at collagen, methods of looking at collagen which are slightly different from the way that we looked at it and came to the same conclusion, but I believe there are some minor differences.

Q That would be El-Torky and Barsky?

A Yes.

Q Okay. You can put that down. Let's -- by the way, it's 11:30. Does anyone want to take a morning break?

(Recessed at 11:35 a.m. and resumed at 11:50 a. m.)

(Exhibit 16 marked for identification.)

MR.YOUNG: Everyone ready to go back on the record?

Q Doctor, as I understand it, the immunofluorescent study that you did for your project with Dr. Madri, is a device to search for collagen on a qualitative level, is that right?

A Yes.

Q It's not a quantitative tool, is that correct?

A It's a semi quantitative tool.

Q Primarily qualitative?

A Semi quantitative.

Q All right. Could, assuming that you were to get possession of tissue blocks from the autopsy of Mr. Rossi, could that study be done on those blocks, could that type of immunofluorescent study be done on those blocks?

A I don't believe it could. The reason is that the tissue blocks were fixed in formaldehyde and as I understand it the fixation by the formaldehyde cross links the bundles of collagen in such a way that you can no longer tell whether it's Type 1, 2, 3, 4 or 5.

So I think the, as I understood this project, the only way it could be done was to obtain the tissue at the time of frozen section as it was sent down from the operating room, to freeze the tumor, and to cut frozen sections on which the immunofluorescence could be done so we bypass the step of fixation in formaldehyde.

Q Do you know whether any of the other collagen stains that you mentioned, techniques for searching out collagen could be used on a fixed specimen?

A The Masson trichrome stain could certainly be done, and that would show the amount of collagen, but it wouldn't tell anything about the various types or the age, et cetera.

Q Let me call your attention to the document which has been marked as Exhibit 16. Let me have you take a look at that, please. Is this the study by Dr. Shimosato and colleagues that we referenced earlier?

A Yes.

Q Do you know Dr. Shimosato?

A Yes.

Q Do you know any of his colleagues?

A It's possible I may have met them. I certainly don't know them, but I do know Dr. Shimosato.

Q Have you discussed this study with Dr. Shimosato?

A Yes.

Q Can you tell us about your discussions?

A They were general. They took place subsequent to the publication of the paper by Madri and Carter, and we briefly discussed the idea of the scar cancer and agreed with each other as to the genesis of the scars.

Q Have you had any other conversations on scar cancer with Dr. Shimosato?

A No, I believe just the one.

Q Now, as I understand it, Dr. Shimosato was trying to determine whether you could look at the extent of fibrosis in a scar cancer and eventually use that to try to predict survival, is that correct?

A Yes. That was, one of the goals of his study was to relate degree of fibrosis to the prognosis.

Q And he, in his studies, also attempted to relate the degree of fibrosis to lymph node involvement, is that right?

A Yes.

Q And he found a correlation, is that right?

A That is correct.

Q But you did not find that correlation?

A We found no correlation. In other words, we were unable to confirm the part of Shimosato's study

which indicated that the degree of fibrosis correlated with the prognosis of the carcinoma.

Q Well, that's two issues. The first one I asked was about his correlation with the grade of fibrosis and lymph node involvement. He found it but you did not, is that right?

A We found a correlation between the fibrosis in the primary and in the lymph node, but we did not find a correlation between the presence or degree of fibrosis and the presence or absence of lymph node metatases. Shimosato did find that correlation.

Q And Shimosato also found a correlation between degree of fibrosis and prognosis, right?

A Yes.

Q And you did not find that correlation, is that correct?

A We did not find that correlation.

(Exhibit 17 marked for identification.)

Q I'm going to hand you what has been marked as Carter Exhibit 17 and ask you to take a look at that, if you would, please. Is this the Barksy Study that you referred to earlier?

A Yes, it is.

Q Do you know Dr. Barsky?

A No.

Q Do you know any of his colleagues?

A No.

Q If you look at Page 413, on the first full paragraph it indicates that Dr. Barsky's specimens were mostly well differentiated bronchioloalveolar carcinomas, is that correct?

A That's his statement. I would have to remind you of what, of the way that I defined bronchioloalveolar carcinoma yesterday and indicate it's defined in a variety of ways. One of the ways, and I think one of the important characteristics of bronchioloalveolar carcinoma is that it's not associated with a scar and this would indicate here that it is associated with scar. So I would say, therefore, it's not a bronchioloalveolar carcinoma, so I presume he means well differentiated carcinoma with a spreading pattern that has fibrosis associated with it. I can't imagine it doesn't have fibrosis associated with it, for him to include it in scar cancer.

So, "bronchioloalveolar" is a term that is used in different ways by different people, and if it's not standardized then we don't know how the term is being used. I would say that he is not strictly following the definition that I used in the fascicle and certainly I would guess that the photomicrographs

illustrating my idea of bronchioloalveolar carcinoma in the fascicle would not coincide with the tumors that he analyzed. So bronchioloalveolar is the word that's there and that's how he characterized them, but, as you indicated yesterday, that classification would not have a consensus.

Q In any event, he appears to be using some sort of a different classification from what you would use for that sub type of adenocarcinoma, is that correct?

A Yes.

Q Could his classification comply with The world Health Organization?

A I don't think so. As I indicated earlier, Dr. Eggleston and I made every effort to try to not state a classification which was different from what the WHO classification would come forth with and they came forth with it subseqent to publication of the fascicle. I think the issue of how much scar you can have in a bronchioloalveolar carcinoma is one of those ideas which would have to be somewhat unsettled.

Q It also appears from that paragraph as controls he used apical scars from TB, is that correct?

A Yes. Well, apical scars. Which were presumed to be from tuberculosis which frequently does produce,

classically produces a sub-apical scar. I presume he is, that the authors are using that term "apical scar" a little built loosely as well. In other words, I think it fair, my reading is they had noncarcinominous scars and they had carcinominous scars.

Q Would you agree that a competent pathologist can, in many instances, identify the remnants of a tubercular scar?

A If it's only a scar, he can't. If there is a granuloma in it, one can infer that it is either tuberculosis or another granulomous process, such as histoplasmosis which you mentioned earlier. If there is no granuloma in it, it's a scar, period, then, the end stage of a process.

Q Is it fair to presume then that when a competent pathologist writes that he has seen a scar from tuberculosis that he has seen evidence which in his mind supports that diagnosis?

A Yes.

Q Do you understand the method that Dr. Barsky used to try to identify collagen?

A Not completely. Generally, I do. I could not, I told you I'm not a chemist and I can't relate to you the nuances of chemistry relating to the method.

Q Can you relate to us your general

understanding?

A Yes.

Q Would you do that, please?

A Basically the authors used antibodies in a way that was similar in many respects to the way that we used them, although they were not quite the same antibodies, at least as far as I can tell. So they did an immunofluorescent study and then they also ground up the scars and attempted to quantitate the types of collagen present. That's something that we did not do. And then they attempted to relate these findings back to the degree of fibrosis.

One of the additional things that they looked at was that they looked at a cell called a myofibroblast, which is a cell that has features of a fibroblast and also features of a smooth muscle cell. It's a cell which is characteristically found in scars of whatever nature. And they used an antibody to the smooth muscle part of the cytoplasm to try to identify those cells because there isn't a good antibody that would identify a strict fibroblast, so they used the pecularity, the muscle antibody to identify something that they called a myofibroblast.

Q Could you see a myofibroblast under the light microscope?

A You can certainly see it. You may have difficulty identifying it as a myofibroblast, but you can certainly see the myofibroblast.

Q Can you see a fibroblast under the light microscope?

A Yes, and the problem is that it would look very much like a myofibroblast.

Q Okay.

A Is that, finished with this?

Q Yes.

A In terms of the methods that they used.

Q Let me hand you what has been marked as Carter Exhibit 18. Would you take a look at that, please?

(Exhibit 18 marked for identification.)

Q Is this the El-Torky study that you mentioned earlier?

A Yes.

Q And El-Torky and his colleagues appear to be from the University of Tennessee, is that correct?

A Yes.

Q Do you know Dr. El-Torky or any of his colleagues?

A No.

Q So I assume you never discussed scar cancer

with any of them, is that correct?

A That is correct.

Q This study involved four cases, is that correct?

A Yes.

Q So that's hardly a representative sample from which you can draw scientific conclusions, is it?

A That's a small sample.

Q That's a small sample. Okay. Then he used as controls, if you look at Page 323 in the top right, four peripheral normal lung specimens?

A Yes.

Q Does that imply to you that he did not use scar tissue as his control?

A Yes, it does.

Q And he concluded, if you look at Page 325 under "Discussion", that "the scar could be the result of a desmoplastic reaction of the host toward the growth of the tumor mass", do you see that?

A I'm sorry. Where are you?

Q Under the first paragraph under "Discussion".

A Okay. I'm sorry. What was your question?

Q The question is, his conclusion is phrased in terms of "could", is that right?

A I think his conclusion is, "meanwhile there

is no clear evidence in our investigations to support the current concept of the scars as a source of origin of the tumor."

Q And then he uses the word "could" to say that the scar could be the result of a desmoplastic reaction, do you see that?

A No.

Q Up above that, the sentence before what you just read.

A Yes. It says, "However, our biochemical and immunohistopathologic studies of four surgically resected cases of pulmonary scar carcinoma suggested the scar could be the result of a desmoplastic reaction of the host toward the growth of the tumor mass."

Q Right. Now, do you know if El-Torky and his colleagues used that same immunohistopathological methods that you used?

A I think they used the same method. You can see there on the same page, Figure 6 is immunofluorescent stain pattern of scar, carcinoma specimen, which you can't read in this photocopy. I mean, you can't see the picture really in the photocopy. I think they made their own antibodies. I think back on 323 it says that they immunized four New Zealand white rabbits with types of collagen so they

made their own antibodies to the different types, 1, 3, 4 and 5.

Q Just like Dr. Madri made the antibodies that you used?

A I don't know whether he used New Zealand white rabbits or not.

Q No, I mean the same concept?

A Same concept, but not the identical antibody.

Q Right.

A In other words, they didn't write to Dr. Madri and ask him to send the antibodies to them. They made their own.

Q Okay.

(Exhibit 19 marked for identification.)

Q I'm going to hand you what has been marked as Carter Exhibit 19 and ask you to take a look at that and identify it. This is Dr. Auerbach's study on lung cancer, is that correct?

A It's one of his studies.

Q We have already discussed that you and Dr. Auerbach know each other, is that correct?

A That is correct.

Q Do you know Mr. Garfinkel?

A No, I do not.

Q How about Verta Parks?

A No, I do not.

Q Have you ever had a chance to discuss this article with Dr. Auerbach?

A Yes.

Q Can you tell us about that discussion?

A Again the discussion was after the publication of the Madri-Carter article, and I can't recall who raised the issue whether he raised it or I raised it. My recollection is that he raised it, but I wouldn't want to swear to that. And he acknowledged that my ideas were interesting in such a way to indicate that he was interested in the subject and interested in a continuing discussion of the subject.

Q Was this one conversation you had with him on the subject?

A Yes.

Q And did you have any other conversations with him on the subject of this article or scar cancer in general?

A No.

Q And he's told you that he thought your study was interesting, is that right?

A Yes.

Q Did he tell you that he agreed with your conclusions?

A He did not say that he agreed with my conclusion.

Q Did he say he disagreed with your conclusions?

A He did not say he disagreed. He just said he thought it was very interesting.

Q Do you know whether Dr. Auerbach has published since this on the issue of scar cancer?

A I think he might have. I think he did. I'm not a hundred percent sure, but I think there are two articles, one, I think another one might be entitled The Relationship to Pulmonary Infarcts, and I'm not sure of the date of that, but my vague recollection is that it's subsequent to 1979.

Q Do you know whether he has ever adopted your opinion on desmoplastic reaction to scars or to cancer?

A I couldn't tell you what his views are at the present time.

Q Do you still see him from time to time?

A I saw him, Dr. Auerbach must be eighty-five, or possibly even more than that. I saw him maybe two, two-and-a-half years ago, and I haven't heard from him. I have asked about him from some people who have come in contact with him, and it's my understanding from them that he has, he's not doing as much as he had been

as late as a couple of years ago, so I don't know his status at the present time. I haven't been in touch with him in two years.

Q You are familiar with this study though, I take it?

A Yes.

Q And in this study, he purported to look at all autopsies from the East Orange, New Jersey VA Hospital from 1955 to '75, is that right?

A Yes.

Q And he's looking for patterns of lung cancers associated with scars, is that right?

A Yes.

Q If you look at Table 1 on 638, indicates he found eleven hundred and eighty-six lung cancers, is that right?

A Yes.

Q And a hundred and eighty-three of them were peripheral lung cancers?

A Correct.

Q Eighty-two with scars?

A Yes.

Q And it appears that the percentage of peripheral cancers with scars was going up during every five-year period that he looked at, is that right?

A That is correct.

Q And if you look at Table 2, it shows that he found peripheral tumors with scars in squamous, with squamous cell carcinoma, do you see that?

A Yes.

Q He found it with adenocarcinoma?

A Yes.

Q He found it with large cell carcinoma?

A I believe that's correct. I can't read that. It looks like a number. Is that an 8, large cell 8?

Q I think large cells 195, mixed type is 8.

A I think mixed type is none and large cells is 8, number of the scar?

A Oh, okay. You're looking at the middle column, I think that's an 8.

Q If you look at 639 at the very beginning of that page, it indicates that "forty-five percent of all peripheral lung careers originated in a scar."

Do you see that, the top left, 639?

A Top left, yes, "forty-five percent of all peripheral lung cancers originated in a scar."

Q Yes then it goes on to say, "In sixty-eight percent of all peripheral lung careers in the 1970-'75 period developed around scars", do you see that?

A Yes.

Q Then if you drop down the page to the end of the first full paragraph, it says "scar cancers comprise twenty percent of all adenocarcinomas of the lung and sixty-two percent of all peripheral adenocarcinomas as shown in Table 2."

Do you see that?

A Yes.

Q And then Table 3 talks about etiology of scars associated with lung carcinoma, do you see that?

A Yes.

Q The last entry shows that in fifteen of the tumors he was not able to identify the scar?

A The etiology of the scar.

Q The etiology of the scar.

A Yes.

Q Okay. He did believe he could identify the etiology of forty-six as an infarct. Do you see that?

A Yes.

Q Nineteen as tuberculosis?

A Yes.

Q One is a granuloma?

A Yes.

Q One is asbestosis?

A Yes.

Q And I assume that you would have no doubt

that if Dr. Auerbach believed that's what he saw his opinions would be worth listening to?

A I would agree that if Dr. Auerbach said that that's what he thought he saw. If I looked at them, I'm not sure I would be able to come up with the same determination. In looking back at the beginning of the article he doesn't really define how it was that he came to the conclusion that it was an infarct, that the scar was due to an infarct.

In other words, if he passed the slide over I'm sure we would all agree that it was a scar as in the article that you cited yesterday, I'm sure if you passed it around to five pathologists and asked them whether it was due to an infarct or tuberculosis, you would get a difference of opinion.

Q But, putting aside interobserver variability for the time being though, I am sure you would agree in general you would respect Dr. Auerbach's pathological diagnosis?

A Yes.

Q Then, if you look underneath Table 3, there is a continuing paragraph. Do you see that? It refers to smokers in the middle?

A Yes.

Q He said in his findings, "Among the smokers

the percent of peripheral lung cancers with a scar showed no increase with the amount of cigarette smoke."

Do you see that?

A Yes, I see it. I'm not sure I understand it. "Among the smokers the percent of peripheral lung cancers with a scar showed no increase with the amount of cigarette smoking." I'm not sure what he means by that. I'm not sure whether he means the incidence of cigarette smoking or the -- perhaps he goes onto explain it here. Okay. The next sentence is, "Among the hundred and sixteen cases forty-six percent of those who smoke less than a pack, forty-five percent of those in the one pack a day and fifty-eight percent of the two pack a day smokers had a scar cancer." That's what it says. I'm not sure what that means except that there doesn't seem to be a correlation or certainly there doesn't appear to be a dose response relationship, but beyond that I'm not sure.

Q There doesn't appear to be a dose response relationship between cigarette smoking and peripheral scar cancer, lung cancer with a scar?

A Right.

Q Do you know of any other studies which purport to correlate peripheral lung cancer with a scar and cigarette smoking?

A I don't know of a study which specifically addresses that. I think that as pointed out in this article that the peripheral carcinoma scars associated are a part of any population of smokers, and presumably as such there would be the general relationship. I'm not aware of another study which picks out this subset of scar cancers and relates it to the smoking.

Q As Dr. Auerbach did?

A As Dr. Auerbach did.

Q On 640 there is another reference to smoking, the first full paragraph on the left column. You have had a chance to look at that?

A Yes, I have.

Q Dr. Auerbach here attempts to relate cigarette smoking with peripheral lung cancer, do you see that?

A Yes, I do.

Q He finds "no increase when cigarette smoking was observed", is that right?

A Well, again, it's not entirely clear. I would read this to indicate to me that all the men were smokers. In other words, he says, "scar cancer was found in six-and-a-half percent of the less than one pack per day", but that would indicate they're smokers, "seven percent of the one to two" and "6.6 percent of

the two plus pack groups", in other words, it doesn't go up with an increase in dosage, but this would indicate to me that, I don't see any statement in the article except for that statement about the one man, the forty-five year-old who had never smoked, that these patients were non-smokers. They're light smokers but not non-smokers.

Q But we don't know from this study whether less than one pack a day includes zero smokers or just light smokers, isn't that true?

A I would assume that it means light smokers.

Q Well, even if your assumption is correct, it still shows that as cigarette smoking increases this study find no increase in peripheral lung cancers, is that right?

A In the specific incidence of this, in the incidence or, let me start over again, it shows no increase in the relative incidence of this subset.

Q As dosage is increased?

A That is correct.

Q And do you know of any other study which purports to specifically relate cigarette smoking and peripheral lung cancer?

A No.

(Exhibit 20 marked for identification.)

Q Dr. Carter, I'm going to hand you what has been marked as Carter Exhibit 20 and ask you to take a look at it and tell me if you're familiar with this study? This is a study called "Scar Carcinoma of the Lung" by Drs. Catherine Limas, Hugo Japaze and Rafael Garcia-Bunuel, is it not?

A Yes, it is.

Q Do you know any of the three authors?

A I knew Dr. Garcia-Bunuel, he died years ago. I also knew Dr. Japaze who was a resident at the time. I don't believe I know Dr. Limas.

Q Do you recall Dr. Garcia-Bunuel's area of expertise?

A It's been between fifteen and twenty years since he died. My vague recollection is that his primary interest was renopathology.

Q And Dr. Japeze or Japeze was a -- ?

A I believe at the time he was a resident.

Q Pathology resident?

A A pathology resident at Baltimore City Hospital which was affiliated with Johns Hopkins, but he was not a resident at Johns Hopkins Hospital.

Q Did you ever get a chance to discuss this study with Dr. Garcia-Bunuel before he died?

A I don't believe I ever discussed this study

with him before he died.

Q How about Dr. Japaze?

A No.

Q Are you familiar with this study?

A I am aware of it. I'm not intimately familiar with it, but I'm certainly aware of it.

Q This study here, purported to have reviewed thirteen cases of peripheral carcinomas thought to be associated with scars, is that correct?

A Yes, it does, but I'll point out that this is February of 1971, it's a long time ago.

Q These, this study concluded that the tumors were arising in the scars, is that right?

A Yes.

Q And if you look on Page 222, the first full paragraph, it lists the etiology that these authors thought to be or the cause of the scar that they thought that they were seeing, does it not?

A Yes.

Q And in four cases they thought they were seeing scars left by a tuberculous infection, is that right?

A Yes.

Q And the remaining cases they said it wasn't conclusive?

A Yes.

Q But they thought they had seen a healed infarct in four cases, granulomous disease in two, and a nonspecific pneumonia in one, is that right?

A Yes, but I would like to point out, as we've talked about, that's an interpretation and, indeed, in Dr. Auerbach's paper that's an interpretation of the cause of the scar. It would be nice if we could go back to all of these studies and, somehow or other, apply some techniques which would allow us to say whether this is a active scar or an inactive scar. The cases that I chose at the time I thought would probably fall into the area of inactive scar, and I would guess that if I got out the eighteen slides and passed them around, that these authors would probably think that they would fit in pretty well with their series. The surprising thing was that it turned out not to be so, so I would say that these authors were talking or reporting in good faith. They interpreted the scars as being the result of an infarct or tuberculosis, et cetera, et cetera, et cetera.

I think that one has to be reminded, however, that that's an interpretation, that the criteria by which they made that determination are not specified and that the interpretation would not be reproduceable.

And I would suspect that if many of these studies were done subsequent to the article by Shimosato that a different interpretation would certainly have been possible, and I think likely, but certainly possible.

Q That's a supposition that we don't know for sure?

A That's a supposition.

Q And we don't have the luxury of going back and looking at these slides at this late date, do we?

A We don't -- presumably one could go back and look at the slides. We don't have the luxury of looking at them to determine the types of collagen, but presumably one could go back and dig out the slides if one of these authors were still around and could do so.

Q But we at least don't have that luxury right now, do we?

A Certainly not.

Q And at least when you knew Dr. Garcia-Bunuel, he was a person whose opinions you respected as a pathologist, is that correct?

A That is correct.

Q Okay. Thank you.

MR. YOUNG: Let's go off the record a second.

(A luncheon recess was taken from 12:45 p.m.

to 1:55 p.m.)

AFTERNOON SESSION

Q Let's go back on the record. Doctor, I would like to hand you Exhibit 5 and have you take a look at that, please. Doctor, these are the records from the United States Navy for 1946 for Mr. Rossi that we discussed yesterday. Have you had a chance to look through these at all?

A Yes.

Q Can you tell us based upon your review of these records what Mr. Rossi's medical condition was in 1946?

MS. WALTERS: You mean when he was discharged or when he was in the hospital?

MR. YOUNG: Based on these records. I asked him based on these records.

A He appears to have had a bronchitis.

Q Okay. And he appears to have one bronchitis or two bronchitis?

A (Pause.) I think he had two bouts of bronchitis.

Q And it appears from the records, does it not, Doctor, if you look at Page 3 of this exhibit --

A I'm sorry, I don't have page numbers on mine.

Q Just the third page, I don't think they are

numbered. It appears that he reported to the Naval Hospital on May 10th, 1946, is that right?

A Yes.

Q And that was his first episode of bronchitis?

A The first in these records, yes.

Q That's right. And then he was discharged, if you look two pages later on May 28th?

A Yes.

Q And the discharge diagnosis is bronchitis acute, is that correct?

A Yes.

Q And then if you skip to the next page it appears that he reported again to the hospital on August 6, 1946, is that right?

A Yes.

Q And if you look three pages later it appears that he was discharged to duty on October 30th of that year, is that correct?

A Yes.

Q And his discharge diagnosis was again bronchitis acute, is that right?

A Yes.

Q And are you familiar with the concept of bronchitis acute?

A As a pathologist or as a physician?

Q As a physician.

A As a physician, yes.

Q Can you tell us what bronchitis acute is?

A It would be an acute inflammatory process primarily relating to the bronchi as opposed to a pneumonia.

Q Okay. And are the two episodes of acute bronchitus disclosed on these records consistent with the development of scarring in Mr. Rossi's lungs?

A It is possible that they might be.

Q Okay.

A I have no way of knowing one way or another. I would say that it was not likely to have produced substantial or large scars because he had some x-rays and indeed he had a bronchogram, and those were apparently technically imperfect, but didn't show anything, so there weren't big scars. As far as small scars, possibly yes, possibly no, I can't tell.

Q We don't have enough information to really determine that issue right now, is that correct?

A In my estimation that is correct.

Q If you will look three pages from the back to an entry dated August 30, 1946. Do you see that?

A Yes.

Q Do you see where it says, "The patient has a

long history of repeated attacks of bronchitis"?

A Yes.

Q Is that entry in the record there referring to "repeated", "a long history of repeated attacks of bronchitis", is that something that is consistent with the development of lung scars for Mr. Rossi?

A I would guess that they would be referring to chronic bronchitis here and that he had repeated attacks over a long period of time which sounds more chronic than acute to me. Chronic bronchitis now would be most commonly associated with smoking. I don't know what it was most commonly associated with back then, and as far as bronchitis, if you try to get at the nature of this bronchitis and the sequelae of the bronchitis within the framework of these records, I would say that if he had a long history of bronchitis, I would presume that would mean years, that the x-ray that was taken in 1946, I believe, as we just discussed, did not show large scars.

So that I would say that this history of bronchitis did not lead to any large scars by 1946. Again, as to whether it produced a fine fibrosis within the lung, can't address that issue. Not enough information.

Q So you don't have enough information to rule

out the possibility, though, that a long history of repeated attacks of bronchitis could result in some lung scarring for Mr. Rossi, is that right?

A It would result in a scarring of the bronchi. I presume you're distinguishing lung scarring from bronchial scar, meaning parenchyma scarring.

Q No, I'm referring to any scarring within the lungs including the bronchus?

A Okay. Well, certainly chronic bronchitis could go onto some fibrosis in the bronchi.

Q Okay. And what about in the lung perenchyma outside the bronchi?

A It would be much less likely. Well, the bronchitis would have to become very severe to lead to the fibrosis in the periphery. However, it is possible that whatever is causing the bronchitis might also cause a pneumonia and, of course, that could lead to pulmonary fibrosis.

Q So it is possible then that a long history of repeated attacks of bronchitis could lead to scarring?

A It's possible.

Q And I would like to call your attention to the fourth page in this document from the first. Start at the beginning and go four pages. Look at about a third of the way down where they talk about the

history.

Do you see that?

A Yes.

Q This appears to be part of the patient history taken in connection with Mr. Rossi's May episode of bronchitis, is that correct?

A Yes.

Q Okay. And that refers here to chronic bronchitis usual childhood disease, pleurisy at ten years of age and I can't see what is that after that, can you read that?

A I can't be sure. My guess is that it says "no TBC" or "history of exposure".

Q TBC would be tuberculosis?

A Yes.

Q Let me ask you about "pleurisy at age ten". Is pleurisy the type of disease that can lead to lung scarring in Mr. Rossi?

A Well, pleurisy is not a disease. It's a symptom of disease, it's a symptom. It's a pain related to pain in the chest usually stabbing in character that's related to breathing efforts, and it would indicate that there was some inflamation on the pleura. What caused that inflamation could be a whole host of things. I would guess that the most likely

possibility would be that he might have some pneumonia, but there are many, many other possibilities. One would be something like rheumatic fever, a variety of other things that could possibly produced it. So it's a symptom, it would be like a cough. Say, could the cough produce it? I don't think a cough could produce it. We would have to infer some other disease process and then infer what that might be.

Q So pleurisy by itself does not tell you or does not indicate that there would be a condition consistent with scarring by itself, is that right?

A Pleurisy by itself wouldn't suggest to me.

Q It's only if we knew what other problem might have led to the pleurisy that we could opine as to whether it's consistent with the scarring, is that correct?

A In my opinion, yes.

Q Let me -- you can put that down. Let me also ask you if, in connection with your review of the medical records entirely in this case, you became aware that Mr. Rossi had a pneumonia sometime in the 1950's?

A I don't specifically remember that. I'm not saying he didn't.

Q I understand.

A I don't specifically remember reference to it in the 1950's.

Q Let me then ask you this question hypothetically. Assume hypothetically, Doctor, that Mr. Rossi had pneumonia sometime in the 1950's, is that condition consistent with the development of lung scars for Mr. Rossi?

A Depending on the type of pneumonia it could be consistent, could be a cause of fibrosis.

Q And let me ask you to assume further that the pneumonia was in fact a psittacosis?

A A psittacosis?

Q Yes. Is that consistent with the development of lung scarring for Mr. Rossi?

A Yes.

Q Thank you. I have no further questions for you, Doctor.

A I wonder if before we finish I could just give you two of the references that I referred to, and, in fact, referred to not entirely correctly. I kept referring to an article by Kuhn.

Q Now, this was in connection with which opinion?

A It was this morning.

Q Okay.

A It was in connection with the scar cancer discussion.

Q Okay. The opinion that Mr. Rossi's scarring was caused by his tumor, is that correct?

MS. WALTERS: I think the specific question had to do with the other people had reproduced his study.

MR. YOUNG: That's what I'm trying to get to.

A Other studies that I referred to. I referred to Kuhn.

Q We asked a bunch of questions. I'm trying to relate this to where I put it in my category.

A Okay.

Q Is this, this is in connection with studies other than the one that you and Dr. Madri did?

A Yes.

Q Okay. On scar cancer?

A Yes.

Q That support your opinion with respect to the scarring seen in connection with Mr. Rossi's lung slides, is that right?

A That is correct.

Q Okay.

A The, what I referred to as Kuhn is actually

Kung, K-u-n-g, and the reference is the American Journal of Surgical Pathology 1985, Volume 9, Pages 391 to 400. And the next one is by Cagle, C-a-g-l-e, et al, and that journal is Cancer Volume 56, Pages 2031 to 2035, 1985.

Q Now, you are reading from a list. Is that from authorities in one of your articles?

A That is a reference list from an article.

Q I just wondered if you could give us the numbers and the name of that article, we can look it up?

A That would be from --

MS. WALTERS: I don't think he can. I think that's a document that I let him look at to refresh your recollection. I don't think he even knows what it is.

Q So we have Kung, American Journal of Pathology, what year was that?

A That was 1985.

Q 1985 and Cagle, et al, from Cancer?

A 1985, also.

Q Is there anything else you would like to add?

A No.

Q Okay.

MR. YOUNG: Off the record while we

switch seats.

(A brief recess was taken.)

CROSS-EXAMINATION

BY MR. KEARNY:

Q Good afternoon, Dr. Carter. My name is Jim Kearny and I represent another one of the Defendant companies in this case, Liggett. I have a few questions to ask you. I would like to start with your description this morning of the stages or phases of development of adenocarcinoma and ask you some questions about that.

First of all, have you, yourself, conducted any research into the phases or stages of adenocarcinoma of the lung?

A Yes.

Q Could you tell us what is, the first phase I understood to be induction of I didn't get the last word that you characterized as the first stage, induction of what?

A Would be induction, period.

Q Okay.

A That stage is characterized, considered to be characterized by an alteration in the genome of the cell, in other words, a change in the genetic make-up of the cell.

Q Now, could you tell us what causes that alteration or what, yeah, what are the causes of that alteration?

A A variety of agents are capable of causing genetic alterations.

Q Could you describe them?

A These would generally be considered the carcinogens, and those would include radiation of a variety of types, and chemical carcinogens, ultraviolet light.

Q Anything else?

A I think that would be a general description. Chemicals is a very broad category.

Q Can endogenous substances cause it?

A Some that are chemicals presumably might be able to do so.

Q And that is chemicals that are produced internally in the body, correct, is that what you understand endogenous to mean?

A It's conceivable that some might be able to carry that in.

Q Is it anything more than conceivable, is it probable that some do?

A I think it's unlikely that they do at a very high level.

Q Okay. Now, how long does the, this altered gene exist, if you will, before the next stage begins?

A Well, to amplify the induction phase, there are, these chromosomal breaks are occurring all the time.

Q Did you explain what you mean by that, they're occurring all the time?

A In other words, all of us probably have breaks in the chromosomes from cosmic rays, radiation, chemicals, whatever, but there are also enzymes that repair those breaks, so that they put them back to normal.

Q Now the chromosomal -- go ahead.

A What I want to say is, it's not just that a break occurs, it's that there are a lot of breaks occurring and that there are so many occurring that the enzymes that ordinarily repair these can't keep up with the rate of breakage. Now, how long does it exist before -- and I'm not sure what you said next, how long?

Q Before the next stage occurs, which you said was the next stage in, the next phase of the development of adenocarcinoma?

A Well, that depends on whether the break is associated with a fatal break which kills the cell,

which is common. If you get chromosomal break because the most likely thing that is going to happen is that you will kill the cell by breaking the chromosome so you have to get a break that is significant, but not enough to kill the cell. That probably lasts for the lifetime of the individual cell in which it occurred. And depending on the lifetime of the cell that you're talking about it would -- it would relate to something that lasted that long. Cells have different half lives.

Q What type of cell would it be that you would have this initial induction in and then I will ask you give me the range of the half lives, the natural life of the cell?

A Are we talking about lung cancer or leukemia?

Q We're talking about adenocarcinoma?

A Adenocarcinoma in the lung?

Q Right.

A I don't know the lifetime. I'm guessing, I would guess it would probably be in the range of a couple of months.

Q So after a cell has been, if you will, inducted --

A Induced.

Q Pardon me?

A Induced.

Q Induced, a chromosomal change has occurred, the following things can happen to that cell: It can be repaired by an enzyme process?

A Right.

Q It can be killed by the chromosomal change itself?

A Yes.

Q It can naturally die away?

A Yes.

Q Anything else that can happen to that cell?

A Well, it can go onto become malignant.

Q Or it can just, I assume, go on to become -- it doesn't inevitably -- I'm sorry. It doesn't inevitably or inelectably become a malignant cell?

A That is correct.

Q It can sit there?

A Well, it's going to die. The cell is -- all of the cells are dying at a, at a variety of rates. The cell is doomed to die when it's started. So it's going to have a natural life of a certain period.

Q Now, just so I understand it, this process that we have just talked about of the genetic change and then the repair goes on whether you're smoking or not?

A When you're exposed to some agent that breaks chromosomes.

Q Or even if you're not exposed to an agent if the break occurs in some other way. The break and the process of repair is something that is common and goes on in the human system all the time?

A No, I think the chromosomal breaks are uncommon. If you were to isolate the cells from all noxious stimuli, but all of us are exposed to noxious stimuli.

Q Can this chromosomal change occur by virtue of genetics, something that is there not by an assault from a carcinogen from the outside?

A I don't know of any circumstance in the lung where that could occur.

Q Can it occur by virtue of a virus?

A It is alleged, it was considered that it might, but as far as I know, there is not substantial evidence, despite considerable effort to demonstrate so, that the virus is responsible for the changes that occur in the lung that lead to carcinogenesis.

Q Do we know how the carcinogen acts upon the cell in order to create this chromosomal change?

A Well --

Q When I say "do we know how", does the state

of science today know how that's done?

A Well, they know that where the breaks are likely to occur.

Q I understand that. Do they know how it occurs?

A Chemically, you mean, what it is that breaks the --

Q Right?

A The strand of DNA, I think, yes. I can't explain it to you, but I think yes.

Q Now, I don't fully understand it either so when you say "chemically" I don't know what distinctions you sought to draw. Do they know it any other way other than chemically?

A Well, the genes are held together by a chemical bond and if what you want me to tell you bonding energies and electron frequencies and all that sort of thing, I can't. But I think there are people who could tell you why it is that there are areas within the genome which exposed to a certain type of chemical compound would tend to break at a certain sequence of basis.

Q Am I correct that you do not contend to know what consituent of cigarette smoking causes this chromosomal change?

A I think there, the last time I looked there was some forty that were capable of creating that sort of change.

Q Now, are you telling me that each one of them separately does it, does science know that?

A I think any one of them is capable of doing it. All forty of them are there, which one happens to do it in a particular cell is not possible to say.

Q Well, or combination happen in a particular cell?

A Or which might,

Q Or whether it's the same all the time?

A Correct.

Q Can you tell in any individual who has contracted adenocarcinoma of the lung when this first phase occurred, this so-called induction process?

A You can make certain guesses. You can't give a date, no.

Q Could you tell us what methodology you use to make certain guesses?

A The guesses are based on the doubling times of the tumor. In other words, if you see how long it takes for a tumor to get twice as large as it was at a previous time, you can, say, calculate how many cells were there at one point and then back, calculate how

long it took to get to that size. That presumes that the doubling times are constant which they almost certainly are not.

Furthermore, it's not possible to recognize an induced but not fully malignant cell. The only way that you can recognize this cell that we have been talking about that's been induced is after the next step occurs where there is enhancement of the process, where the cell is forced to multiply so that the daughter cells have an opportunity to reproduce this abnormality and presumably to enhance it. To the point where it then becomes recognizeable as an individual cell which is neoplastic.

Now, if you enhance these cells without the induction you don't get a neoplastic cell. If you enhance them and then give the inducing agent, you don't get a neoplastic cell. You have to initiate, then secondly promote or enhance or drive the cell into reproduction in order for the cell to go from a normal cell to a neoplastic cell.

Q I'm going to get to that I think. Let me go back to, you were trying to describe for me how you would determine when the first inducted cell that resulted going through the phases that you have articulated for us in an adenocarcinoma in an

individual, and you said that you would go through this process of doubling time. Now am I correct that that leads you to a guesstimate of when the first cell, altered cell occurred?

A That would, if you went back to the first cell, yes.

Q When in relation to that time did the first cell become induced, can you tell that?

A From induction to the first doubling?

Q Right.

A The --

Q The first doubling I understand is what you get from the doubling time analysis?

A Right. That would be the outer limits of it would be the life span of the cell.

Q Of the cell?

A Yes.

Q And you told me, what is the range of life spans of cells assuming they get through all the others, they're not killed off naturally?

A The normal life span, I think, is a couple of months.

Q Now, did you tell us yesterday, and I don't want you to repeat your testimony, but I want to be sure I understand it, did you give us an opinion

yesterday about how long it took from the time that Mr. Rossi's adenocarcinoma would have been clinical to the time that it was, from the time it became subclinical to the time it was observed was approximately two years, is that right?

A I said it would have been at least two years.

Q At least two years. Do you have an opinion as to when the first cell doubling would have occurred in Peter Rossi's cancer?

A One could back-calculate and I think you would have a very broad range. I think it could possibly go back as many as fifteen, twenty years.

Q And on the other side what's the short part of the range?

A Probably in the range of probably two to five years. My guess is that the doubling time was not constant. I think at the end the thing was really growing very rapidly.

Q Let's see if we understand.

MS. WALTERS: Wait a minute. Are you finished your answer?

THE WITNESS: Yes.

MS. WALTERS: You cut him off, but I guess he was finished.

MR. KEARNY: I'm sorry if I cut you off.

I took my eyes down for a minute. I'm trying best to follow all of this. And I also understand that you're not looking at the witness, so many times you may think I'm cutting him off.

MS. WALTERS: He said a word.

MR. KEARNY: I'm not concerned about your objection, so don't worry about it.

Q I want, again, to make sure I understand this. In the various phases of the production of an adenocarcinoma that you gave us this morning, which is the phase that we have just established to be within the range of fifteen or twenty to two to five years for Peter Rossi?

A We haven't gotten to that yet.

Q Okay. Good. Let's then proceed through that.

A We have done induction. We were talking about the second stage which you can call enhancement or promotion.

Q Can you explain "enhancement phase" for me?

A Well, same as promotion, in other words, something comes along that can drive the induced cell to proliferate, that is, to form a lot of daughter cells at a relatively high rate, at an increased rate.

Now that may be the same thing that caused the induction or it may be something different.

Q Okay. Explain to me what you said there are things that can cause this enhancement. What "things" can they be?

A Promotion, can we use enhancement promotion interchangeably?

Q Yes, I understand that.

A What things? They could be the same agents that caused the induction, all of them.

Q Now we have gone through what they can be?

A Right.

Q In addition to them, anything else?

A In addition to those, the things like asbestos fibers apparently can act as promoting agents. Inflammatory reactions can result in promotion.

Q What else?

A That's sort of the broad categories, things that cause inflammation. I know asbestos fibers have been studied intensively. I presume that some other fibers might also act as promotors, but I can't quote which ones might.

Q Okay. Can coal dust?

A I don't know that coal dust does very much.

Q When you say "inflammatory reactions", can

you describe what those inflammatory reactions are that can cause this promotion of an induced cell?

A Anything that would incite injury to the normal cells, such as bacteria. If somebody got pneumonia it would cause increased proliferation of the cells in the vicinity.

Q Any other disease processes that could cause this, other than pneumonia?

A Anything that causes pneumonia.

Q I'm not a doctor, what other things cause pneumonia and only one of any kids have had pneumonia so far.

A Bacteria, virus, toxic fumes, tuberculosis.

Q Anything that's ingested?

A Certainly if you vomited and aspirated that would do it.

Q What happens, anything ingested that's not vomited and aspirated?

A I'm not aware of any in that category.

Q Can an ingested carcinogen cause the first induction?

A I think that's a subject of debate. Yesterday, we talked about that study by the Kanisawa, I believe, where he did show that that occurred.

Q Right.

A Whether that occurs in other situations, I don't know.

Q So my question was, assuming for the moment that it can occur in the induction phase, can ingested carcinogens also create or cause or be a causative factor in this promotion phase?

A I don't --

MS. WALTERS: In lung cancer?

MR. KEARNY: We're always talking about adenocarcinoma of the lung and this is the Haines case and we're at this deposition.

A I don't know the answer to that. I would guess it could, but I really don't know for sure.

Q Am I correct that in the, there is no way you have of telling, science has of telling, whether or not in any individual person who has been diagnosed as having adenocarcinoma of the lung whether or not the induction and enhancement phase is caused by the same causative factor or agent, isn't that right?

A That's correct.

Q How long, Doctor, does this enhancement or promotion stage usually last?

A It lasts a variable period. The limits would not be as well defined as they would be for the induction period which is limited by the life span of

the normal cell. Presumably it would have to occur during the time that one of the cells was induced before it died, and then a variable number of cell cycles or reproductions would have to occur before these induced cell became fully neoplastic. And that apparently is a matter of chance to a great degree, and, therefore, the more times it reproduces the more likely it is to become neoplastic.

Q Now, you've just introduced a new term to our lexicon here. When you say "cell has become neoplastic", can you relate that to your five phases of the development of adenocarcinoma, which phase would you say the cell or cells had become neoplastic?

MS. WALTERS: Five phases or four?

MR. KEARNY: Four or five stages, we'll get them. I haven't added another phase. I'm not competent enough to do that.

A I would say that it would occur after the process of induction and sufficient promotion to transform it into a malignant cell has occurred and that the, as soon as that occurs the cell becomes immortal. In other words, we get away from a cell which has a defined life span into a cell which you can put into culture and it will keep growing as long as you keep the circumstances in which it's growing

satisfactory for the cell. If you put a normal cell into culture it will live its life span, then it will die.

One of the tests for determining whether or not a cell has become neoplastic is to put it into culture and if it keeps growing forty, fifty, generations, then you know it has become neoplastic. So, at that point is where it becomes neoplastic. If that answers --

Q Does the neoplastic cell occur sometime during this process of promotion, does it occur during the process of what you call "the growth stage", that is the multiplication of the cells?

A It occurs, it is the culmination of promotion.

Q The culmination of promotion. And you would say that, therefore, is either before, it is before rather what you termed earlier this morning as this growth stage?

A Right.

Q Am I correct that once that happens that does not mean that malignant cancer, adenocarcinoma, will inelectably follow?

A It means that it will follow unless something dramatic occurs to stop it from following.

Q Okay. Would you say at that stage that it is irreversible?

A Yes.

Q It's irreversible. And what is it, that dramatic would have to happen?

A Well, if you take it out.

Q Anything short of that?

A That would stop it. If for some reason or another you're able to kill it at that stage.

Q That would be, again, a medical intervention that you're talking about?

A No, not necessarily. It's possible that the cell might have changed in such a way that it has alerted the immune system to the fact that it's totally abnormal. And that the normal cells of the body come in and kill it off.

Q And I don't know how to put this, but now you're talking about the common response of the immunological system of the body?

A Yes.

Q When a cell or group of cells run amok. There is a system in the body to attack that and that happens commonly?

A Most of the time. In other words, you can think that all of us sitting her now are forming little

malignant tumors or tumor cells and our bodies are presumably killing them off.

Q That is, in fact, what's happening?

A I think that's what's happening right now.

Q And I would assume we're in bad shape if that immunologic system stops operating?

A It only has to miss one.

Q As you get older does the immunological system deteriorate?

A The immunologic system gets worse and the ability to repair DNA breaks also decreases.

Q Can you give me an age for that, when does that begin to occur, that is the difficiency in or the reduction in the effectiveness of the immunological system and the reduction in the effectiveness of the DNA repair systems?

A I think there is a gradual decline of the ability to repair DNA. That's a pretty general slope.

Q When does it begin, sir?

A I think it probably begins in our teens.

Q And --

A And that's the reason that we uncommonly see tumors in a younger age group. We usually see it in older people.

Q And the reason is that the repair systems are

more effective when you're younger?

A Yes. The ability --

Q Does the reduction in the DNA --

MS. WALTERS: Wait a minute?

A Go ahead.

Q Does that reduction in the effectiveness of the DNA repair system decrease in a linear slope?

A Yes.

Q You were going to tell me what the ranges, when the immunological systems relevant to this begin to deteriorate, how quickly do they deteriorate?

A They deteriorate latter and to a much more variable degree. In other words, there is not a straight line slope related with it. In other words, the immunologic function of many older individuals is perfectly intact as far as we can tell, whereas in somes other it falls off.

Q And it can be affected by disease, I guess, Aids is the first thing that comes to mind on the part of the layman. Isn't that a dimunition in the immunological system? I withdraw the question. I don't want to get into another area.

What types of things, what are the factors that account for the variability in the reduction of the effectiveness of the immunological system?

A I don't think they're well understood, at least not by me. I know they are quite variable.

Q So let me go back. I asked you the question, when this induced cell that has gone through promotion is in the back end of the promotion, becomes neoplastic, will that ineluctably lead to carcinoma of, adenocarcinoma of the lung? And am I correct your answer is yes, unless it is destroyed by the immunological systems of the body?

A Or someone reaching in and kills it or something else kills it, actively kills it, yes. Because now it has become an immortal cell that can continue to grow and doesn't stop growing according to normal stimuli.

Q So, when I asked the question how long would this phase of ad -- the development of adenocarcinoma last, the promotion phase, what I should have asked, and I'm now going to ask is, can you tell us all the things that can happen to this collection of cells that have now become neoplastic, and have yet to go into this growth stage. One of the things that can happen is the immunological system of the body come to bear on it and eliminate it and the other, are there any others, other than it marches along?

A Well, it's removed.

Q Okay.

A It's removed either by design or by accident.

Q Now, the next stage, I have in my notes that you mentioned "growth stage, multiplication of cells." Can you describe for me, what is that stage called?

A That's the growth stage.

Q What happens, explain to me what happens in that stage?

A The individual cells just keep dividing and the mass of tumor cells gets gradually bigger and bigger and bigger.

Q At that stage is this mass capable of being invasive or does that happen in the next stage?

A At any step of the way while it's growing, well, if it just grows, then it's confined and it would eventually get big enough where it would probably cause some symptoms, show up on a chest x-ray, and if it were just growing, then the surgeon could go in and take it out and it would be cured.

Q And because it is not yet gone to the next stage, which is the stage that you characterize as the stage in which the cell acquires the ability to spread through human tissue?

A To invade normal tissue.

Q Okay. So another thing that can happen to

the neoplastic promoted cell is that it just gets bigger but it remains in the same place until such time as it becomes clinical and is removed?

A Yes.

Q How long would you say that stage would last until such time as those cells acquire the ability to spread through human tissue?

A That's quite variable time. Some tumors never acquire the ability to invade the normal structures. Others acquire at a very early stage. The outside limits of the size that you could attain would be about forty doublings from the original cell.

Q How long would that take?

A For it to double forty times?

Q Right.

A That would depend on the doubling rate and the doubling rate has, I have seen as long as two hundred fifty days, so it would be forty times two hundred fifty days. For adenocarcinomas they tend to be on the long side. I think the lower range of an adenocarcinoma would be fifty days and the upper range would be something like two hundred and fifty days. So it's a very broad range there.

Q Now, what is it that makes this mass -- let me withdraw that. So I assume there are some in this

stage, some groups of cells that never acquire the ability to invade human tissue and there are others that do?

A Yes.

Q Can you explain to me what makes one group acquire the ability to invade human tissue and the other group not acquire the ability to invade human tissue?

A I obviously can't do that. There are a lot of things that we know about at that stage and some of the things that are important are the ability to break down collagen.

Q I'm sorry, break down what?

A Collagen. So that you, can the cells can get away from where they're normally found. There are, another is the cell acquires the ability to make a receptor so that it can clamp onto collagen and it can sort of march its way along through the collagen. Those are some of the things. We don't know all of the things. Obviously that's a very critical point.

Q We don't know what gives the cell the ability to break down the collagen or to permit one of its receptors to clamp on to collagen?

A We don't know what does that. And, in fact, the reason that I hesitated over one of the statements

that Mr. Young read to me this morning, over the induction phase or the genetic change being stable, is that this is an example of instability. In other words, the tumor cell first acquires the ability to get, to grow, and then it starts acquiring other things. So it's not stable. It's unstable. And some of the cells are going to acquire the ability to invade the normal tissues. And those normal tissues would include the pulmonary parenchyma. It could include the bronchus. It could include the blood vessels. It could include the basement membranes by which it is bound.

Now, one of the things that may happen as the tumor has grown into this mass and has acquired the ability to invade, is that once it gets out of the area in which it is started, it may then attract an immunological response.

Q And then the same thing would happen that we talked about before, the immunological system would kill it off?

A No, at this point the immunologic system probably can't kill it because there are too many of them in that it takes over two thousand lymphocytes to kill one tumor cell, so if you're dealing with one or two or three or four tumor cells, you can get enough

lymphocytes in there. If you send through a thousand, then you would have to get too many lymphocytes in there to kill it. But what might happen at that stage is that the inflammatory cells might come to that point because of the anti-antigent that the tumor cells are displaying. When they come to that point they would behave like they did in an inflammatory response in that that could lead to the production of scar.

Q Let me, if the mass does not acquire the ability to spread through tissue, it -- well, withdrawn. I think we covered that. It just gets bigger. Does it ever stop growing? If it doesn't get the ability to move out at that stage, if it doesn't get the ability to invade other tissue, does it ever stop growing?

A The net growth may stop. In other words, if it slows down to the point where the cells are losing their blood supply as fast as they're being replaced, you may have a stable period, but, in general, no. It continues to grow.

Q Now, the next stage you said was the tumor cells acquire the ability to grow at other sites?

A Right. In other words, the tumor cell has grown, it's invaded into a blood vessel, it has gone through the blood vessel, and then it has to go through

another blood vessel and it has to be able to live in another place. A place distant from the environment in which it grew up.

Q Now, what gives the cells the ability to do that?

A Nobody knows.

Q All right. The last two phases that we just talked about, which is, in fact, the last three phases, multiplication of the cell, then when the cell spreads into human tissue, and the third one we just talked about, do they come all after the first doubling?

A Yes.

Q Okay. So the only thing that comes before the first doubling would be the induction phase and the promotion phase?

A Induction and promotion.

Q Okay. Both of which are reversible by virtue of a number of reasons which we have talked about?

A Well, either of which.

Q Either of which are?

A Either of which can be terminated. I don't think you can reverse them. In other words, if you've got induction, if you've got the chromosome break, the chromosome break is going to be there and it's going to be abnormal, that cell may die off and that takes care

of it. I don't think you can put the -- you are not going to put the chromosome back together the way that it should have been.

Q Let me ask you, I tried to look last night at some of these sputum cytology studies that are around. And am I correct that in some, let me put it this way, am I correct that a malignant cell as diagnosed in one of these sputum cytology studies, can whatever that condition is, I'm not talking about that cell itself, can be reversed if you remove the carcinogen?

A I'm not sure it reverses it. It may go away, which is not precisely the same. From a functional standpoint, the organ goes back, the organ reverses, something may happen to get rid of these neoplastic or cancerous or precancerous, cancerous cells. That's not to say those same cells turn back into normal cells.

Q Correct. That's what I mean.

A They may die out.

Q The condition reverses itself?

A The condition may become reversible, but the cells are not.

Q There are studies that show that?

A Yes.

Q And that would be also the case with respect to the development of adenocarcinoma?

A I would guess that it probably would. The only studies that I know of relate to squamous cell carcinoma. That's really the only type of cancer that has a recognizeable phase before invasion occurs. I presume the same thing applies to adenocarcinoma, but it would be much more difficult to demonstrate that.

Q Ah-hum. Okay. I don't want to spend very much time on this, and I don't intend to, but I just have a few questions about the phases of cancer development for squamous, and I understand that they are, that you classified them as, am I correct, precarcinoma, preclinical, and clinical?

A Yes.

Q And you have talked about the average amount of time for each of those three stages in the course of the development of squamous cell carcinoma?

A Yes.

Q Could you tell us what those periods of time are?

A I don't remember. I have written them down, I would be glad to refer to them, but I don't remember. It's a long time.

Q In the precarcinoma stage I understand it you include metaplasia, there is something that you have as atypical metaplasia. What's the difference between

metaplasia and atypical metaplasia?

A I discussed that yesterday. Atypical is a term that's used by different people in different ways. And I explained to him when I was at Hopkins "atypia" meant neoplasia, what we thought was precancerous or non-invasive cancer. At Yale we use "atypia" to mean a cell which we think is responding to inflammatory stimulus, and we use the term "dysplasia". So atypical metaplasia is the same as dysplasia, which we think is a cancer cell that is on its way to becoming a full-fledged malignancy.

Q What is hyperplasia?

A Hyperplasia just means more cells than normal.

Q Dysplasia?

A Dysplasia is what we just talked about.

Q Do you use the term "cancer-in-situ"?

A Yes.

Q What does that mean?

A That means cells that have gone on to become malignant and the part that we talked about, but have not yet acquired the ability to invade through the, into the normal tissues.

Q All right. And as I understand, under this hypothesis or theory cancer-in-situ does not

necessarily result in malignant cancer?

A Does not necessarily result in a tumorous mass with invasion and metastasy.

Q Thank you. And so in that sense that condition can be reversed if you've got cancer-in-situ?

A As we talked about before the condition can be reversed if something comes along and kills those cells off.

Q In adenocarcinoma do you find metaplasia, hyperplasia, dysplasia, and cancer-in-situ?

A You can't relate it directly to the adenocarcinoma, as you can in the squamous.

Q Now, can you tell us what are the causes of metaplasia?

A Inflammatory noxious agents that would include in any of the things we talked about.

Q That's certainly is not limited to people who smoke cigarettes?

A No.

Q Hyperplasia?

A Same.

Q And if the causative agent is removed in either one of these two, the condition abates?

A Yes.

Q If the causative agent is reduced does the

condition abate?

A If it's reduced enough.

Q And if the causative agent isn't reduced or eliminated at all, in some circumstances the situation can still abate, isn't that right?

A I don't think so. I think if you continue to apply the agent in the same dose on the same schedule, you will tend to get the same response unless you change something else.

Q And this we already said, dysplasia and cancer-in-situ can be reversed if you remove the agents that are causing it?

A Yes.

Q And it can abate if you reduce that agent, can it abate if you reduce that agent?

A I presume if you reduce it enough it can.

Q All right. Am I also correct that not all, the condition of metaplasia doesn't always progress to hyperplasia?

A Hyperplasia and metaplasia are really two fundamentally different things. Hyperplasia means that there are more cells. Metaplasia means that the form of the individual cell has changed.

Q Okay. Let me --

A Now, there may be more of them, or there may

not, but they're fundamentally different processes.

Q Am I correct that not all hyperplasia progresses to metaplasia?

A Yes.

Q And I guess it would then be not all metaplasia progresses ineluctably to dysplasia?

A I think very little of the or very few of the examples of metaplasia progress to dysplasia.

Q What happens to that metaplasia?

A It either persists or the noxious stimulus ceases and it returns to normal.

Q And not all cancer-in-situ processes to a malignant tumor, as you have defined malignant tumor?

A Yes.

Q And am I also correct it is clear from the data that you know of that invasive cancer may occur in the absence of these sequential progressive changes?

A I'm not clear which sequential changes --

Q I'm talking about the sequential changes of hyperplasia to metaplasia, displasia, cancer-in-situ?

A Well, with adenocarcinoma you don't have those stages.

Q Okay. What about with squamous carcinoma? Isn't it the case that even that can occur without these sequential changes?

A It can certainly occur where you can't find those changes or evidence of those changes. Or those changes may occur very rapidly. Whether or not it occurs in the total absence of those changes, I'm not sure, but it certainly may occur without demonstrable evidence of those changes.

Q Is any part of your opinion today based on, your opinion in this case based on your knowledge on oncogenes?

A I certainly can't deny that I know something about oncogenes. I would say that that is background information that would reinforce my opinion, but it isn't the primary basis for my opinion.

Q Let me ask you a few questions about that then. Can you briefly describe what is an oncogene?

A An oncogene is a gene which when put into a reproducing cell line causes it to become malignant.

Q Causes the cell line to become malignant. What is the term, can you explain the term an "oncogene expression"?

A Well, oncogene expression just means that the oncogene is a gene on the chromosome and oncogenes, in general, are those genes that are the genetic code for important parts of the cell. In other words, they tell the cell to make something that's significant. If it

were an insignificant thing, it wouldn't change the cell very substantially. So that the expression of the oncogene means that something has made the oncogene have the cell make that particular product. Does that answer your question?

Q Ah-hum.

(A brief recess was taken.)

Q Am I correct that how an oncogene comes to be expressed remains unclear?

A Yes.

Q And I take that from one of the articles you wrote on ovarian adenocarcinoma and I would like you to explain what that means. Why and how an oncogene comes to be expressed is unclear in the development of adenocarcinoma?

A Well, because the oncogene may be present but for some reason or another the cell may not be making the product that the oncogene codes for. Does that explain?

Q Not really. Not enough for me anyway. Can you give me some more explanation on that?

A Okay. The oncogene is a gene which is either identical to or very similar to, but subtly altered from a normal gene. The oncogene is in the DNA. Now, for something to happen the DNA has to be transcribed

to RNA. In other words, there is a messenger substance that goes into the nucleus, picks up the information and then moves out in the cell and starts the cell making a certain thing and, let's say -- let's see, what's something that would be simple to think about. Let's say, well, this wouldn't be an oncogene. All right, it's telling the cell to make some part of the membrane which does a special thing.

Q Okay.

A Now, the oncogene is going to be on the nucleus in the DNA on the chromosome and it's going to stay there. There are some things that come along that tell that cell to transcribe a lot of messenger RNA and make a lot of this product or there are periods when the oncogene stays in the DNA and it's not transcribing messenger RNA and it's not making a lot of product although the product that it made before may still be there, so you may be able to find the product or you may be able to find the messenger and from knowing either of those two, then you know the oncogene is in the DNA. I can diagram it for you probably a little bit more simply if that might help.

Q Can a tumor develop or a tumor occur in the absence of the expression of oncogenes?

A I don't know of a tumor that doesn't express

at least one oncogene and, in fact, most tumors express a lot of oncogenes.

Q Dr. Carter, were there any causative factors, in your opinion, other than smoking cigarettes in Peter Rossi's development of adenocarcinoma?

A I didn't find reference to any specifically.

Q So there were none?

A That is correct. There were none.

Q So, had he stopped smoking, he would not have gotten adenocarcinoma from cigarette smoking, is that not right?

A I think it would depend on when he stopped smoking.

Q Had he stopped smoking after having smoked for ten years?

A I'm sorry. When did he start smoking?

Q I believe you testified that the basis of your opinion in this case is that he smoked for thirty plus years and that he was a heavy smoker, is that right?

A I believe that the reference that I saw in the history was that he smoked two packs a day for thirty years.

Q And you said yesterday you based your opinion on a sixty-pack year smoking history?

A Somewhere in that range.

Q Based on those assumptions had he quit ten years after he started smoking, would he, is it your opinion that he would not have gotten his lung cancer?

A I think it's less likely that he would have gotten his lung cancer.

Q Is it more probable than not that he would not have gotten his lung cancer?

A I'm sorry?

Q Is it more probable than not that had Peter Rossi quit smoking at ten years after he started that he would not have gotten lung cancer?

A Please bear with me. I'm trying to short through the double negatives in the question. Let me answer it this way. If we assume that he had about a third of the exposure that he had, it would put him in the moderate smoker range which would have reduced the likelihood that he would have gotten a lung cancer. Now, if you then multiply out a reduction by twenty years, then I happened to catch on CNN, The National Cancer Institute, now says that there's a thirty to fifty percent fall-off in risk at ten years, that's data that I haven't seen, but it was on CNN. That would put it into a markedly, it would decrease the likelihood of his having had cancer in 1982, but, in

other words, it's a, I think it's an unanswerable question. Here you have somebody who demonstrated that he did get lung cancer. Now, can you take that away? I don't think there's any way to answer that. I think if you take a population of people like Mr. Rossi who only had a third of their exposure and decreased that or stopped them from smoking over twenty years, there is no question that you would markedly decrease the incidence of lung cancer in that population of people. Given an individual who's demonstrated that he can go on to lung cancer, I don't know that you can put the genie back in the bottle. I don't know the answer to your question in a very strict sense.

Q Well, you did say that at some point when you asked me what, at what point do you want me to have you assume that he quit. You said that you thought it would, quitting would have an impact. Let me ask you this. Is it more probable than not that he would not have gotten cancer had he stopped smoking one year after he started. Can you tell me that?

A Is it more probable than not?

Q Yes.

A Yes.

Q All right. Is it more probable than not that he would not have gotten his lung cancer, let us

assume, Doctor, that he started smoking at age eighteen, all right, and he quit, smoking two packs a day and he quit at age twenty-two, is it more probable than not that he would not have gotten lung cancer?

A It's more probable that he would not have had got lung cancer.

Q You have no trouble if you were advising a patient or a friend or a family member to stop smoking after five years of smoking to tell that person if you stop smoking, more probable than not you won't get lung cancer when you're fifty-five, sixty or sixty-five than if you keep smoking. You don't have any problem giving them that type of advice, am I correct?

A I wouldn't say that. I would say that, "If you keep smoking you're more likely to get it." I think for the individual who has smoked, who subsequently develops lung cancer, that it's not a mystery why they developed the lung cancer.

Q Okay. If somebody who was smoking for five years asked you today, "If I stopped now can I avoid getting lung cancer from my cigarette smoking?" what would your answer be?

A There is nobody who can guarrantee you that. I can't tell you that "You're not going to get lung cancer."

Q Can you tell me that it's more probable than not that I'm not going to get lung cancer from my cigarette smoking?

A I can say that it's in that group that more people would not get lung cancer than would get lung cancer.

Q Can you tell me --

A But if he we go twenty years and the person says, "Doctor, you told me if I stopped smoking I wouldn't get lung cancer. I stopped smoking I got lung cancer, I'm going to sue you", I certainly wouldn't put myself in that situation.

Q So you couldn't say that more probable than not you are not going to get lung cancer from your cigarette smoking, you wouldn't feel that you could say that. A medical doctor could not say that to a patient who inquired about what their chances were of avoiding cigarette smoking if they stopped smoking?

MS. WALTERS: He answered that question as to himself.

MR. KEARNY: I withdraw the question.

Q Doctor, let's continue on. If Peter Rossi had stopped smoking two years after he started, would you say more probable than not he would not get lung cancer at the end of his lifetime from cigarette

smoking?

A Well, I'm not sure I can follow this line out. If we talk about a group of people, we can say that if they smoked for only one year or two years or that the smaller the dose that they got, the less the chance that they will develop lung cancer. The sooner they stop, the better off they are. No matter when they stop, they will decrease the risk of the entire group for getting lung cancer. That doesn't apply to an individual person who we know has got, died from lung cancer. So I can't come back, "what would have happened if", I don't know the answer. I don't, I can't tell you that. I can tell you going forward, but we can't go back.

Q Why is it that you can't tell me? Withdrawn. If you can tell me for the group, what their chances are of getting lung cancer if they quit, why can't you tell me for an individual that would fall into the group?

MS. WALTERS: He answered that question.

MR. KEARNY: He told me he couldn't say it.

Q Tell me why?

A Why?

Q Right.

A Because you're starting from a different point. If you start with a group of people who do not have lung cancer, you can make a mathematical calculation of how many of them might develop cancer given a certain set of circumstances and follow it for a certain period of time.

If, on the other hand, if you start at the other end and you say this person has lung cancer, at what point could we have said that he would not have developed it. I think there are too many uncertainties to --

Q Is that because you don't know which persons or individuals in the group, you know that a certain number of them will get the disease, but you don't know which ones in the group are going to get it, is that right?

A Yes.

Q And so, therefore, had Mr. Rossi stopped smoking in 1964 you cannot say whether or not he would have gotten lung cancer later on in his life, right?

A Is that a question?

Q Yes.

A Yes, I can't say.

Q Had he stopped in 1970, or '71, you couldn't say whether or not he would have gotten lung cancer

from his cigarette smoking?

A Yes.

Q You can't say that, science cannot permit you to say that?

A Right.

Q Doctor, doesn't all of the data support the proposition that were Peter Rossi to stop smoking ten years after he started that he would not have gotten lung cancer?

MS. WALTERS: What data are you referring to? I object to the form of the question.

MR. KEARNY: He can say he doesn't know or no. He can say he doesn't understand me.

A I would say that we know Mr. Rossi got lung cancer. We can't redo history. We have to deal with --

Q I'm asking you, I'm posing a hypothetical to you, though. Let me take a person, all right, who is a male, who is a smoker, two packs a day, okay, commences smoking at age fifteen to eighteen, smokes for ten years, two packs a day, and quits. Doesn't the epidemiological data, the animal experimental data, your human sputum cytological studies, all support the proposition that more likely than not that smoker would

not get lung cancer in his lifetime from cigarette smoking?

MS. WALTERS: Just so I can place an objection on the record, this witness -- I have let you go along on this for awhile. You know we have a reduction of risk expert who has reviewed all the data that does not support your question, and this witness is not being offered as a reduction of risk expert. I have let you go along to a certain point, but I think it's starting to get objectionable. How long do you intend to pursue this line of questioning, Mr. Kearny?

MR.KEARNY: I find you're coaching inappropriate and I ask the witness for a response.

MS. WALTERS: I don't know what data you're referring to. Our expert, who is offered on the subject disputes what you're saying. This witness isn't being offered on the subject. You're talking about a hypothetical about, quote, "all the data" and you won't even outline for the witness what data you are referring to.

MR. KEARNY: Are you directing the

witness not to answer?

MS.WALTERS: I don't think I can.

MR. KEARNY: He'll answer it now or before the jury.

MS. WALTERS: I don't think he is going to answer it before the jury because he's not being offered on this subject.

A I would go back to what I said. We know Mr. Rossi got lung cancer. So we have to take him out of discussion. If you want to give me a hundred people like that, I can say that their risk of lung cancer would be less and considerably less than that of a hundred people who kept smoking at the same rate for another twenty years. I can't tell you what might have happened to Mr. Rossi if circumstances were changed.

Q That being the case, I assume you can't tell us what part of his smoking, the first ten years, the middle ten years, or the last ten years, made, contributed the most to his development of his adenocarcinoma?

MS. WALTERS: Again the --

MR.KEARNY: No speeches, just object.

MS. WALTERS: I am objecting.

A I would say that, yes.

Q Why don't we go on here. You mentioned Dr.

Auerbach's Beagle Study yesterday. And you mentioned that you, I believe, saw the dogs?

A I saw one of the dogs who had smoked. He wasn't smoking at the time.

Q So you did not see the apparatus?

A I saw the apparatus. I didn't see it in operation.

Q So you didn't actually see a dog with the trachial opening?

A I have seen photographs and, in fact, a movie of it, but, I saw one of the dogs.

Q Do you rely on that research, on the results of the research in connection with your testimony in this case?

A Those dogs, in general, developed squamous abnormalities and not adenocarcinoma. So, in that sense, I'm not relying on it.

Q What were the results of that test?

A They found that the dogs, the beagles who smoked for a period of time developed changes in their respiratory tree which were considered to be pre-cancerous, that were fully malignant. Those changes were predominantly of the squamous type, although I believe there were some changes out in the periphery of the lung, but as I recall none of them

developed, none of them died of their cancer. It was a short-term experiment.

Q Do you believe that what happened in that study in the beagles is also what happens in human lung cancer?

A Oh, I think there are some similiarities and there are certainly some differences. They were dogs. They smoked almost continuously and the period of time was relatively short. Dogs don't live nearly as long as humans do so the time of the exposure was quite limited. I think that extrapolation is always somewhat risky as we have just talked about, and I think that,, it's not surprising that those dogs had what were interpreted as early stage lesions rather than full-fledged cancer.

Q When you mentioned the term "extrapolation", what do you mean?

A To say that the dogs smoked for a year, therefore, what would have happened if they smoked for thirty years. Well, dogs don't live for thirty years, so we can't say.

Q Can you extrapolate from that dog study to what happens in human beings who smoke?

A I think you can extrapolate some of the acute phase of smoking.

Q What do you mean by the "acute phase"?

A In other words, the early years. I don't think, certainly they didn't smoke for thirty years, so you can't get information.

Q Do you, let me put this hypothetical to you. If a cigarette was developed and tested in Auerbach's beagle dog system and there were no precancerous changes, could you extrapolate that to humans and determine that cigarette would have the same effect, which is no precancerous changes in humans?

(The pending question was read.)

A I don't think you could fully extrapolate it. I think if you found no precancerous lesions, I think it would be a very interesting observation and worth pursuing. One of the ways to tell something is precancerous is to follow it for a long time. Of course, dogs don't live a long time by human standards so you couldn't say that you followed the dog for two years and he didn't have cancer then when humans live for a much longer period of time. So it's an interesting idea, but I'm not sure it would prove your point.

Q But you couldn't conclude from that that the cigarette smoked by humans would cause no precancerous changes, right?

A In part due to the fact that you couldn't follow them long enough.

Q Couldn't follow the dogs?

A Right.

Q Do you rely on mouse skin painting animal experiments at all for your opinions in this case?

A In part.

Q What part?

A To indicate that some of the substances are capable of inducing tumors in a very finite situation.

Q When you mean "finite situation" what do you mean?

A I mean that you can say that the only agent which is being applied is X.

Q Is the mouse skin painting model more closely analogous to the human system than Auerbach's inhalation model?

A I think it's -- no, it's not more similar to the human situation.

Q In fact, it's less similar or more dissimilar?

A More dissimilar.

Q At present is the mouse skin painting model viewed as a valid research tool to determine carcinogen?

A Mice are not used anymore than necessary for two reasons. One for humane reasons, and secondly, because they're terribly expensive. There are other tests that are used mainly to do with mutagenicity of the agent and cell lines and in bacterial lines which of cheaper and have assumed the role of a standard rather than using live animals.

Q Are you aware of the dissimilarities in the mouse skin painting model and the human system of smoking, do you know what they are?

A I certainly know some of them.

Q What are they?

A First of all, it's skin and not lung. Secondly, it's a mouse and not a human, and thirdly, it's a single agent rather than numerous agents. Fourth, the time of observation is very brief rather than very prolonged.

Q Would you say the route of administration is different as well?

A Yes.

Q Would you say the substance on which the, the substance that is being tested is different namely cigarette smoke condensate is different from whole fresh smoke?

A In some ways, yes.

Q And that the dose is different?

A The does is different.

Q Can you and also that the mice are bred to be susceptible to developing skin carcinomas, is that correct, the mice used in these studies?

A I don't know.

Q Are you aware that the, are the defense mechanisms different?

A In mice versus man?

Q Yes, that come into play with lung cancer in man and that come into play, if they do at all, in the mice skin paintings, cigarette smoke condensated on the backs of mice?

A I think they would be, Certainly would not be identical.

Q Do you know how they differ?

A No.

Q And what about the nature of the tumor, is the tumor on the backs of the mice resulting from the application of the mice in this protocol of cigarette smoke condensate and squamous carcinoma and adenocarcinoma?

A A squamous cell carcinoma.

Q Did the 1964 Surgeon General's Report rely on mouse skin paintings as part of the basis for its

conclusion that cigarette smoking was a causative factor in lung cancer?

A I don't recall.

Q Now, I believe you said that you relied on the mouse skin paintings and you may not have -- to some extent in your opinion. To what extent, in what respect do you rely on the mouse skin paintings again?

A I rely on them to indicate that there are certain substances which stated in the literature which are found in cigarette smoke which are known to be carcinogenic.

Q Let me ask you this hypothetical question. Assume for a moment that none of the mouse skin paintings ever resulted in any tumorigenicity, the production of carcinomas on the backs of mice, never happened, in all of the protocols of cigarette smoke condensate that never happened. Would that change your opinion?

A No.

Q Your opinion would still be that cigarette smoking causes lung cancer?

A Yes.

Q And that's derived, and that's, I guess, it's because -- well, why is that?

A I answered that question yesterday.

Q I don't want you --

A Maybe we can read it back.

Q I will cull through it. I don't want you -- so that if, today, cigarettes were, cigarette smoke condensate from cigarettes today were applied to backs of mice in the normal protocol and resulted in no tumorigenicity, no cancer production on the backs of mice, you couldn't conclude that that cigarette would not cause lung cancer, is that right?

MS. WALTERS: He just answered that.

Q Did you just answer that?

A I'm sorry. Would you read it back for me.

(The pending question was read.)

A Yes.

Q You were in medical school when, in 1958 or '57, did you begin?

A 1957 to 1961.

Q You talked yesterday about the, I believe personal and professional evolution of your opinions with respect to cigarette smoking and lung cancer and I would like to go over them if I can a bit. At that time were you taught anything about cigarette smoking and lung cancer?

MS. WALTERS: Asked and answered.

A I don't remember having heard it.

Q So you don't recall what your teachers said or what your textbooks may have said about that?

A Yes.

Q What textbooks do you recall using that dealt with cancer. Let me just go back. Did you study cancer at all?

A Yes.

Q Do you recall studying cancer?

A Yes.

Q In what courses did you study cancer?

A Studied it in internal medicine and in surgery.

Q Okay. And am I correct that you also did a surgical residency?

A I was an intern and a first year resident in surgery.

Q Did you also study it in pathology courses?

A Yes.

Q And you don't remember what was said about cigarette smoking and lung cancer in medical school in any of these courses if anything was said?

A I can't recall.

Q Okay. Can you recall what texts were used?

A I'd be glad to go back and look them up, but right off the top of my head, I can tell you that the

clinical medicine text was Harrison. Harrison.

Q Harrison?

A And several others. He was the first editor. The surgery text. I can't remember what surgery text I used during my time in surgery, during my time in medical school. I have had several and I can't remember which one it was. The pathology textbook was Anderson.

Q Now, in any or all of those courses did they discuss the causes of lung cancer?

A Well, that's over thirty years ago now. I'm going to have to tell you that I don't remember specifically, that that's been over thirty years ago.

Q Okay, fine. I'm just asking for your best recollection. Did they tell you when you were examining a patient when you became an intern and then a resident whether you should, did they instruct you to take a smoking history from patients?

A Again, that's twenty-nine years ago. I don't remember.

Q Did you, do you recall taking smoking histories from patients?

A Yes.

Q When you were an intern?

A Yes.

Q And again, when were you an intern?

A 1961 to '62.

Q And that was at Johns Hopkins?

A No, that was at Ohio State University in Columbus, Ohio.

Q I didn't spend much time with the resume. And then you went to Johns Hopkins after that?

A No, after I was an intern I was a first year resident in surgery at Ohio State University.

Q That was '62 to '6 --

A '63. Then 1963 to 1965, I was at Walter Reed in Washington in the army. From 1965 until 1968 I was a resident in pathology at Hopkins. From 1968 to 1969, I was a fellow in pathology at Memorial Sloan-Kittering in New York, and from 1969 to 1977 I was back at Hopkins on the faculty.

Q Did you know why you were asking these patients to give their smoking history?

A I think that the primary reason was that in surgery most of them were going to have general anesthesia. It was felt that smoking history would impact on their response to inhale anesthetic agents.

Q Any other reason?

A Very few of the rotations I was on had patients who had lung cancer. Most of the rotations

were general surgery that had to do with gastrointestinal lesions, so that the smoking history was not particularly pertinent to them. In terms of the specific reason and identifying people at risk for lung cancer, I don't recall that that was, that that was so.

Q Let me ask you --

MS. WALTERS: He hasn't finished the answer. "I don't recall that that was a" and then you interrupted.

Q I didn't think you had anything else to say. I'm sorry?

A I was finished.

Q Okay. If, Doctor, it had been proven in 1958, when you started medical school, that cigarette smoking was a cause of lung cancer, would your medical school professors know that?

(The pending question was read.)

A I think my medical school professors were very good and I think they would have been aware --

Q You just don't recall?

A -- of publications.

Q And do you have any recollection that they told you at the time you were in medical school that cigarette smoking was a cause of lung cancer?

A You're asking me from a vantage point that would indicate it would be incredible if they didn't say that. I don't remember whether they told that or not.

Q And you don't recall whether you had occasion to tell patients that? Let me withdraw the question and ask this question. Who were your professors at Ohio State that would have taught you about lung cancer in any of the courses we talked about?

A I didn't have any teachers as such. I was a resident, an intern and resident at Ohio State. The person who was involved in pulmonary surgery there to the greatest extent was a person by the name of Karl Klassen.

Q What about in medical school, who were the professors that would have taught you those subjects?

A I can remember one of the surgeons was Dr. Alfred Blaylock.

Q Can you remember any of the others, in surgery, pathology or internal medicine?

A Pathology, everybody taught everything pretty much. Pathology, internal medicine, I think, probably Richard Sheppard.

Q Okay. Did there come a time that you began to advise patients with respect to smoking and their

health?

A No. I should point out that I stopped seeing patients in 1963.

Q So at no time, there was never a time that you advised patients on smoking. Did you and your peers in Ohio State and then at Walter Reed, prior to that in medical school at Johns Hopkins, rely on the tobacco companies to provide you with information about cigarette smoking and health?

A No.

Q Do you recall in the time you were in medical school that there was a scientific debate over the question of whether or not smoking caused lung cancer?

MS. WALTERS: Are you representing to him that there was or are you asking if he recalls it?

Q I'm asking whether you recall?

A I recall that there was a debate. I recall that the debate sort of came to a head in the '60's.

Q And what period in the '60's?

A I would say the early to mid '60's.

Q Were you surprised by the results of the Surgeon General's Report?

A I'm not sure "surprised" is a word that I would use.

Q Was the community of your colleagues and peers at that time at Walter Reed, would you say they were surprised by the results of the Surgeon General's Report?

A I think in 1964 everybody was concerned about Viet Nam and not the Surgeon General's Report and lung cancer.

Q Did you have any knowledge as to why the Surgeon General's Advisory Committee, is it committee or commission, was formed in 1962 ultimately reporting their findings in January of 1964?

A No.

Q Tell us what you recall of this debate over the issue or questions as to whether or not cigarette smoking causes lung cancer when you were in medical school and then in your internship and residency?

MS. WALTERS: If I have the years right, it was mid-'60's.

MR.KEARNY: He said it came to a head at that point in time.

A I think part of my recollections are colored by the reading of the history at the time, so I'm not sure I can.

Q Meaning your present reading?

A Right.

Q Or recent history, reading of the history?

A Of the history of it. My recollection is that there was a growing body of evidence to suggest that lung cancer was related to cigarette smoking and that a number of studies were carried out and, indeed, I think that the topic is still actively scrutinized and that the bulk of the studies began to show that there was a serious relationship between the two, and as more and more studies were designed, it seemed to become more and more clear that this was a very substantial relationship.

Q Have you actually reviewed, yourself, any of the underlying epidemiological data or studies that are referred to in the Surgeon General's Reports?

A I have read some of the papers, yes.

Q Is a smoker less likely to get lung cancer from cigarette smoking if the smoker smokes a low tar cigarette rather than a high tar cigarette?

A I don't know.

Q It struck me during the course of the deposition yesterday that I didn't understand your use of the term "reasonable degree of medical certainty" or "reasonable degree of medical probability", and I wanted to see if I could probe that a little bit to find out what that means.

First of all, I guess it means something less than certainty, a hundred percent certainty?

A I have always had difficulty with the term as well. I think that "medical certainty" to me means is it sufficiently likely that you would act on the information.

Q Thank you. It does not mean to you, or -- withdrawn. Is that definition that you have just given me, would you consider that a generally accepted definition in the medical community?

A I don't know.

Q Can you tell me if you have ever, tell me where you got that definition?

A Oh, I have struggled with the idea considerably. All my colleagues struggle with this "reasonable medical certainty" as opposed to "reasonable medical uncertainty", and where one draws the line. I think it's a difficult and a judgmental --

Q In any event, you will agree with me that it is not simply the weighing of evidence? Let me withdraw that. It is not simply in a situation, the situation where there is uncertainty and a situation in which there is evidence supporting two theories, okay? The use of the term "reasonable medical probability" is not simply a determination of which evidence outweighs

the other evidence, it's not just simply determination of the preponderance of the evidence, but rather there must be some objective standard that tells a doctor whether there is enough evidence on either side of the question for him to conclude that there is reasonable medical certainty?

MS. WALTERS: I'm going to object to the form of your question. You used two different terms in the same question to mean the same thing.

A First of all --

MR. KEARNY: That may very well be the case and I apologize.

Q If you do not understand the question, I will assume you will tell me?

A I do understand the question. First of all, it's not simple at all. You can't use the word "simple" in it. I think if there are two groups of or two bodies of evidence, neither of which seems to have considerable support or neither of which has very much support, then if you weigh those two types of evidence and one is higher than the other, that still doesn't tell you that you're reasonably certain. You do need evidence of a type which is more compelling and enough of it and the definition of "enough" is what we all

struggle with in order to reach a decision of reasonable medical certainty.

Q Okay. Can we take our afternoon break?

(Recessed from 4:10 and resumed at 4:25 p.m.)

CONTINUED EXAMINATION

BY MR. KEARNY:

Q Am I correct, Dr. Carter, that had Peter Rossi stopped smoking prior to the induction of the cell that ultimately resulted in his adenocarcinoma, that he would not have gotten adenocarcinoma from cigarette smoking?

A Yes.

Q Now, assume the induction was caused by a carcinogen related to his smoking, by the inhalation of a carcinogen from his smoking. If Peter Rossi had stopped smoking after that induction but before the promotion stage, aren't I correct that he would not have gotten adenocarcinoma from cigarette smoking?

A Yes.

Q And the same is the case if the induction that ultimately resulted in his adenocarcinoma, was caused by some other agent or carcinogen unrelated to smoking?

A I'm not clear on your question.

Q I'm asking you to assume that the induction that ultimately resulted in his adenocarcinoma was not caused by his cigarette smoking was caused by something else and after that induction he stopped smoking cigarettes before the promotion stage, that it's more likely than not that he would not have gotten this adenocarcinoma from cigarette smoking?

A Yes.

Q Now, assume that the induction was caused by his cigarette smoking and that the promotion was caused by his cigarette smoking, but he stopped smoking at that phase of the development of this adenocarcinoma he would have avoided the cancer, isn't that right?

A I'm sorry. Could you restate it?

Q Okay. Assume that the induction and that the promotion was caused by carcinogens from his smoking but he stopped smoking after that stage. Isn't it more likely than not that it would not have developed into the adenocarcinoma?

A I don't know that.

Q All right.

A I would say the answer is likely, if you assume it had gotten started then the answer would be no.

Q But we're assuming it got inducted, it got promoted, we assume the carcinogen was then removed. Isn't it more likely that it would not have developed into a adenocarcinoma?

A No, I don't think that follows. Once induction and promotion start, then ball is rolling.

Q In the opinion you just gave, would it make any difference when the induction and promotion that ultimately resulted in his adenocarcinoma had occurred?

MS. WALTERS: When in his lifetime?

A When? No.

Q I will vary the question just a little bit. Assume that the induction occurred, that promotion occurred, but this was, but prior to the neoplastic change that we spoke about, he stopped smoking. Isn't it more likely than not that he wouldn't have gotten lung cancer?

A You can't have all those things. If induction and promotion have occurred, then you have started the neoplasm off on its way. Then it's just a question of time before it becomes evident.

Q Yeah, but this is before it has acquired the ability to invade human tissue, it's before it acquired the ability to grow to other sites. It's at a time when it can be attacked by the immunological -- by the

well, I will leave it at that. Had he stopped smoking at that time, is it more likely than not that he would have avoided his cancer?

A I don't think you can say that, no.

Q Can you say one way or the other whether he would have avoided it?

A I would say, if you would take as a given that it's induced and promoted sufficiently, then, you know, you can say it's either promoted or not, but if you tell me it's already been promoted then you finish those two phases and it's on its way and, yes, at that point technically he has cancer.

Q What was the time period from promotion and when the tumor became clinically observable in the Peter Rossi case?

A I don't know. I gave you the inner and outer limits of that.

Q You did. Okay. What if you removed the carcinogen, stop the smoking, if you will, halfway through the promotion stage?

A Well, if it's not fully promoted then it won't become cancer.

Q Okay. And how long is that, is that -- is the period from the time it begins the promotion phase to the time it becomes fully promoted, as you say, is

that period encompassed within the timeframe that you gave us earlier in the deposition? Do you know what I mean by that?

A No.

Q Okay. Is the, you gave us a timeframe from inducement to, I guess it was clinical observation of the tumor, and you said it was from two to five years to fifteen to twenty years?

A No, that's not --

Q Could you explain? I think there was confusion as to what you said.

A I will be glad to. Induction occurs in the cell. The cell has a finite life. Promotion has to occur while that cell is alive or the cell dies and the induction dies with it.

Q Right.

A And then the next cell, another cell may become induced and during that cell's lifetime it must be promoted or it dies. So, it is a continuing process.

Q But we're not concerned -- I'm sorry, I didn't mean to --

A The promotion has to occur in the induced cell.

Q Right. We're not concerned with an induced

cell that died off because that didn't cause Peter Rossi's adenocarcinoma, correct?

A That is correct.

Q We're concerned about the one that you contend did start the process that caused his adenocarcinoma, that's what we're dealing with, right?

A Right.

Q What we don't know, when that, am I correct, that induced cell was induced?

A Yes.

Q We don't know when it began the process, correct?

A Yes.

Q Now, to make things clear, so we all understand each other, what I'm asking you is, from that time, right, when the induced cell that started this process off to the time that his tumor became clinically observable in this case, how much time elapsed?

A I would say that it required somewhere between thirty doubling times. Anywhere in the range of thirty to a maximum of forty, less than forty probably in the neighborhood of thirty, thirty something, doublings and that those doublings might

have been as brief as fifty days or as long as two hundred and fifty days.

Q Okay.

A Now, I think, if you do that arithmetic it comes out to about the years that I gave you, but it's certainly simple enough to do the arithmetic.

Q There's just another piece of uncertainty that you may be able to resolve. On the one hand you talked about the induction promotion process that you think goes on with adenocarcinoma. On the other hand we've talked about the hyperplasia, metaplasia, dysplasia phases of the development of the squamous cell carcinoma. Does the induction promotion process that you talked about also occur in the development of hyperplasia?

A Hyperplasia can occur completely independently.

Q Okay. Does induction --

A Of either induction or promotion.

Q Does induction promotion relate at all to these phases of the development of squamous cell carcinoma?

A Yes.

Q When does that occur in these phases?

A It --

Q The phases are hyperplasia, metaplasia, displasia, cancer-in-situ, malignant cells, as I understand it.

A Your question is?

Q Where does this concept or mechanism of induction and promotion occur, if it does at all?

A Induction occurs in a way that you can't see as either hyperplasia or metaplasia. An agent which was promoting could produce hyperplasia and/or metaplasia. And if it were acting on an induced cell, then that cell would go on to become displastic. If it were acting on a non-induced cell, that cell would just become either hyperplastic or metaplastic. And if you withdraw the stimulus, then it would return to normal.

Q So, where you have displasia, you will necessarily have the presence of inducted and promoted cells?

A Yes. Where you have metaplasia and hyperplasia you have promoted cells but not necessarily induced cells.

Q All right. But with dysplasia that's reversible, remove the agent and it goes away?

A The cells die off.

Q So that means even induced and promoted cells

die off?

A Yes. Well, let me correct that. They do die off if you were to put them into a tissue culture medium where everything is favorable and there are no noxious stimuli, they wouldn't die off like normal cells they would continue to reproduce. But in the situation where they do die off in the body, there may be many other factors acting to actively kill them.

Q Okay. What was, what's the time period in your estimation or in your opinion from the time of the production of the neoplasm or the occurrence of the neoplasm to the time of clinical observation of Peter Rossi's adenocarcinoma?

A I don't know that. It would be within the ranges that I gave you.

Q Can you tell me where within those ranges?

A No, you know, I'd be sure it's within those ranges and beyond that I wouldn't be certain.

Q So you can't say it's ten years before observation?

A I can't tell you that.

Q Whether it's five years before observation?

A Right.

Q Okay.

MR. KEARNY: I have no further questions

and pass the witness.

Thank you very much, Dr. Carter.

CROSS-EXAMINATION

BY MR. ALLINDER:

Q Doctor, I'm Bill Allinder, an attorney for one of the Defendants in this case.

You have used the term in -- or terms in your testimony "clinical" and "subclinical"?

A Preclinical.

Q Preclinical. And I assume that the term clinical means clinically observable?

A Yes.

Q And what specifically does that mean "clinically observable"?

A The clinical phase was defined as the phase in which the patient felt ill or had a cough or some symptoms that would be related to the presence of the neoplasm in the lung, and that would be either cough or coughing up blood, or chest pain, or fever due to the pneumonia associated with it, or whatever symptoms that would bring him to medical attention, or a lesion that was evident on a chest x-ray.

Q In this particular case when did Mr. Rossi's tumor become clinical?

A I would say that it became clinical at the

point where he started having symptoms, which was not too long before he came into the hospital.

Q You don't recall specifically from your review of the medical records when that may have occurred?

A I think it was a reasonably brief time. I would have to check to get anymore accurate. In other words, month-to-month rather than years.

Q You also, I think, had mentioned earlier that adenocarcinoma typically has a long doubling time?

A Yes.

Q And in this particular case because of the size of the tumor, that is described in the gross autopsy as well as the distant metastases, you thought perhaps this tumor had probably doubled a little quicker in its latter stages of development, is that correct?

A Yes.

Q Now, you were describing for Mr. Kearny before I think there were five stages of tumor formation?

A Yes.

Q And --

MS. WALTERS: Four or five? Was it four?

Q I think it's five. Do you agree with me, Doctor, there are five. I suppose we can tick through them again.

A I think it's five. Well, there's induction, promotion, growth, invasion and growth in another site or metastasis, so five.

Q Metastasis is the fifth. In this particular case, when during this process do you think the doubling time quickened, shortened?

A During the final phase.

Q During the phase five which is, as I understand it, is in the clinical phase as opposed to the preclinical?

A Yes, clinical.

Q At stage three which is the growth stage, at that point in time the tumor or the neoplasm is preclinical, is that correct?

A It may be unless you happen to get a chest x-ray.

Q So when we're talking about stage three for this particular cancer, it is more likely that that neoplasm was doubling at a slower rate?

A Yes.

Q You had given us, I think, a fifty day to two hundred and fifty day window or variation between the

doubling times for adenocarcinoma?

A Yes.

Q So I suppose from your testimony you're telling us from the time this tumor was clinical in its last stage that the doubling time was probably on the short end?

A Yes.

Q Down towards fifty?

A Yes.

Q Back when we're in stage 3, more likely than not it's toward the longer end, two hundred fifty?

A Yes.

Q Okay. And I think you also said that it takes thirty to forty doublings from the end of phase two before it becomes clinical?

A Yes -- no, until you die.

Q Until you die?

A Right. But unfortunately, the clinical phase is usually between thirty and forty.

Q Mr. Kearny had asked you about the time that it would take for a tumor to go from stage one to becoming clinically observable and you had given him a range in years again based upon the variation in doubling time that was available for adenocarcinoma, is that correct?

A Yes.

Q But considering the fact that you think that this tumor was doubling at a slower rate toward the slow end in its preclinical state, isn't it more likely that the period of time from stage one to becoming clinically observable was longer as opposed to shorter?

A Certainly it's possible. I don't know how to tell you whether I would say that I think the latter part of the disease was more probably than not associated with a more rapid growth. Whether or not you can extrapolate back and say the earlier phase was slow, and then it took off, or that it was something that went through all of the phases at a very rapid pace, I think is speculation.

Q Perhaps I misunderstood you a few minutes ago. I thought you told me that it was more likely that the tumor was doubling at a slower rate in its preclinical stage?

A I think it was growing more slowly in its preclinical stage than at the very end. Now, whether or not that slower was fifty, two hundred fifty, and the terminal rate was toward the shorter time, I don't know. I would be guessing, and I don't have a very firm basis on which to guess. So, I'm not trying to evade or mislead you, I think what I said was that when

you asked me, was the final stage of the tumor associated with more rapid growth, I think that's true. If one goes back to the doubling from one to thirty, I don't think we have any information on that. I think it would be slower than it was doubling at the end, but which of those rates it was taking, I just wouldn't know how to guess.

Q Is that information scientifically unknowable?

A I think it's unknowable, yes. The only way to determine an accurate doubling time is to have an accurate measure of the size of the tumor at one point, wait a period of time, and determine that the tumor has increased in size and then make the calculation for doubling of mass and come up with a figure in terms of days. If you don't have two points, if you're working with only one point, then you can't determine what the doubling time was. If you look at something that's spreading all over the body, living in the lymphatics of various organs, it suggests that it's a tumor that's growing very rapidly. To go back in time and say it started off and it escalated at twenty-seven doubling times, I think it would be highly speculative.

Q I think that you had told Mr. Kearny earlier that if the stimulus, the cause of the initiation was

removed after stage two, after promotion was completed, that the removal of the stimulus would not affect the outcome of that particular neoplastic growth, is that correct?

A Yes.

Q I think you used the words "off and rolling" "or the ball was rolling" by that time?

A Yes.

Q By the end of promotion. I guess in my layman's terminology I would say that the carcinogen or more than one carcinogen had done its work by that point?

A Yes.

Q You had used a term a couple of times in your testimony, I think it's "proliferation"?

A Yes.

Q What do you mean by "proliferation"?

A It's the increase in the number of cells from one to two to four to eight to sixteen to thirty-two.

Q As you use the term then it's essentially the same as cell division?

A Yes.

Q It is one cell dividing into two cells. Is that the same as mitosis?

A Mitosis is the process by which a cell

divides from one into two. And proliferation also implies that you are increasing, that the division is going on more rapidly than in cell death, so that you're accumulating more cells rather than being in a steady state.

In other words, if you have one cell it divides and forms two, and one of them dies, you still have one. But if you are undergoing mitosis at a rapid rate and one goes to two and both of them stay alive and both of those divide to make four, and it increases exponentially.

Q So you were using the term to really mean increased cell division or increased proliferation?

A Yes.

Q More than what you would expect to see in the ordinary circumstances in a particular tissue that you're viewing?

A Yes.

Q As I take it that different cell tissues divide at different rates?

A Yes.

Q And also it will divide at different rates depending on the age of the individual concerned?

A I think that the age has relatively little to do with the rate at which the normal cells turn over.

Q I was using age very, very broadly to suggest that you would find, for example, more cell proliferation or division, rapid division in a particular organ of a young than you would in a fully grown adult, as an example?

A One would think that that would be true, but it's not a major difference. I think the major difference in people is that they get older is that it's not that the cells aren't turning over, but that the cells are dying a little bit faster.

Q But when an individual is growing, there is an accumulation of additional cells, obviously, to accommodate for the growth?

A Yes.

Q That was the only point I was trying to make. And I think that I had asked you a minute ago, you said a minute ago that within an adult different cells divide at different rates?

A Yes.

Q For example, there is, I suppose, no cell division in the brain tissue and perhaps very rapid cell division in skin?

A Yes.

Q When cells divide it's a part of the mitotic process there is a duplication of the entire DNA of the

cell, is that correct?

A Yes.

Q And do mistakes spontaneously occur during mitosis in the sense that a mutation or a genetic abnormality results?

A Well, I'm not sure mistakes occur. Abnormalities certainly become evident.

Q I'm using the term "mistake" in the sense they're not an exact duplication of the genetic material so that there is a gap, there is something missing, something has been put in the wrong place, it's not an exact duplicate?

A That occurs.

Q Can abnormalities, genetic abnormalities occurring from normal cell division, mitosis in normal cells, ever result in a malignancy?

A I don't know.

Q Is it possible?

A Certainly it's theoretically possible, but with the variety of agents that we know that can cause breaks, it would be difficult to exclude that there was no cause for the break other than a mistake on the part of a normal cell. I don't think we see mistakes occurring. I'm trying to think of a situation where something that could be called a mistake happens. None

come to mind.

Q So as far as you know there are no genetic abnormalities resulting from normal cell mitosis, am I understanding you correctly?

A I think there are not abnormalities that result that don't have some cause. I think if you're given a normal cell and left alone and allowing it to continue to divide, I don't think it would go on to become a malignant cell, no.

Q Perhaps I have misunderstood your answer. You were not saying then that abnormalities cannot occur spontaneoulsy during normal cell division, but that absent some other stimulus they can proceed to a malignancy?

A No, I'm not saying that. What I'm saying is that there is a cause.

Q Then I am confused.

A There is a cause.

Q You do not, I don't mean to belabor this, I'm trying to make sure I understand what your position is. You do not think then that genetic abnormalities occur through normal cell division?

A I think, all right, can I back up a little bit to try to explain --

Q Certainly.

A -- what I mean. If you say "normal cell division", that means that there is a division as a result of the, division of the DNA that's present in a cell. Now, if there's an abnormality in the DNA, it will be magnified by the process of division and if there is an abnormality in a chromosome, it may make it such that only part of the chromosome goes to one cell and more than a normal amount goes to the other cells. So, the normal division is bringing out an abnormality.

But if you start off with all normal chromosomes and just divide them, then you will have two normal cells. So I'm not saying that division doesn't, at the end of division you do have abnormalities, but what I'm saying is that you start off with an abnormal situation which becomes amplified as a result of the division and that the chromosome doesn't just --

Q I think I understand you now.

A -- blow apart.

Q Let's talk about a latter example. Start off with a normal cell as far as we know there is nothing wrong with the genetic material, you have a complete set of good DNA and it undergoes normal cell division. We get two cells that are exact duplicates, there are no defects in them, is that what you're saying?

A Yes.

Q There are no mutations. No abnormalities can occur to normal cells undergoing ordinary mitosis?

A Unless something has happened to them.

Q No external stimulus?

A No external stimulus at all.

Q That is correct?

A I think it highly unlikely that you would have a change.

Q Let's take the, let's go back to your other example. Let's take an abnormal cell. And you indicated that mitosis on an abnormal cell might enhance the abnormality or change the abnormality in some way so that the two daughter cells, if we can call them that, may not be identical to each other and may not be identical to the cell from which they came from?

A Yes.

Q It's also, let me ask you a question, is, does mitosis in genetically abnormal cells often result in the death of the cells themselves?

A Yes.

Q I want to ask the mitosis question again to make sure that we're on the right track. During mitosis, part, as part of the process of mitosis there is a complete replication of the DNA?

A Yes.

Q And then as the cells divide there is a complete set of DNA, the original DNA in both new cells?

A Normally.

Q Normally. And when I was asking you about genetic abnormalities during mitosis that would include genetic abnormalities occurring during DNA replication in ordinary cells without any external stimulus?

A I'm not sure I'm clear on what you're asking me.

Q Okay. I thought we were both together before and now I think I have gone back.

A I followed you a long time, but I'm not sure I'm clear.

Q Mitosis includes DNA replication, that's the process, of course, of making a new set of the DNA?

A Yes.

Q A second set?

A That is the prophase.

Q And as the cell splits one set of the DNA goes with each cell?

A Yes.

Q And with a normal cell undergoing ordinary cell division we don't see abnormalities in the

daughter cells, is that your opinion?

A Yes.

Q When you were talking with Mr. Kearny before you were discussing with him the decline in efficiency of the DNA repair mechanism in the human organism as part of the process of aging?

A Yes.

Q You said it starts in the teens and is a linear slope that goes down over some period of time. Do I assume that in the normal individual that it is of one hundred percent or the maximum capacity at the teen, during the teen years?

A Yes.

Q Do you know what percentage it is at at age forty or age fifty in the ordinary individual, in another way I'm asking you for how steep the slope?

A How steep is the slope? I think the slope is not very steep. In other words, still at our age, we're repairing most of our DNA, the great majority of our DNA, so we're talking about very small percentage decrease.

Q Can you put a figure on it?

A I don't know the number. I'm sure it's known, but I don't know that.

Q I think in response to a question from Mr.

Kearny I think you said it was beyond the ability of science to determine whether or not the causative agent for initiation and the causative agent for promotion in the same neoplastic cell were the same?

A In a clinical situation.

Q In a clinical situation. Does it follow from that that science also cannot tell what the specific causative factor for initiation is?

A Yes.

Q And similarly, for promotion?

A Yes.

Q You mentioned in your testimony when you were talking about induction, and I think you mentioned the different causes of induction, you talked about chromosomal breaks?

A Yes.

Q Is that correct? And you described as the potential causes of induction any substance or condition that could cause a chromosomal break?

A Yes.

Q And I think that was pretty much the limiting parameters of your answer?

A Yes.

Q Anything that can cause a chromosomal break can cause initiation?

A Yes.

Q So do I take it from that that things that don't cause chromosomal breaks can't cause initiation?

A Yes.

Q Are there other types of genetic abnormalities besides chromosomal breaks?

A Well, I think the fundamental thing is the break then it comes back together and it may come together with either extra bases or lost bases. In order to change a gene you have to at some point separate it or break it. I'm not quite sure we're on the same wavelength on this question.

Q Is transformation a genetic abnormality or cause of genetic abnormality?

A Yes.

Q Is that different from a chromosomal break?

A To get a transformation you have to break something, take the piece out, break it again and put the piece in a separate place so that breaking is part of the process.

Q Would a point mutation be a chromosomal break?

A Yes, you would have to remove, break the chromosome, take one base out, put another base in, and then close it up.

Q Okay. I'm not sure that there are other kinds of genetic abnormalities, but if there are any, would there also been chromosomal breaks?

A They involved the breaking and remaking of chromosomes.

Q Are you familiar with a theory of carcinogenesis mechanism known as spontaneous cancer?

A No.

Q You haven't heard that term?

A No.

Q If I can describe it in a slightly different way, are you aware of the theory that mutations occurring in normal cells undergoing normal mitosis or cell division can become malignant and lead to cancers?

A I'm not sure I know that theory.

Q I will go back a little bit further in the deposition. I'm trying to wrap up as quickly as I can. You had, I think, described to Mr. Young pretty early on in your deposition how you reviewed the pathological material for Mr. Rossi?

A Yes.

Q And I think you said that you looked at it through a light microscope?

A Yes.

Q Did you and I think you also said you did not

use electron microscopy?

A Yes.

Q Did you used polarized light?

A Yes.

Q You did?

A Yes.

Q Did you see anything through the polarized light that you did not see through the light microscope?

A There were occasional bits of material that might possibly have been silical-like, very occasional bits. I used the polarized light to specifically look for asbestos bodies and I didn't see any.

Q The silica bits, are those aso called silicates, is that right?

A Yes.

Q Were they in proximity to the tumor?

A There were very few of them and they were mainly in the lymph nodes.

Q Did they play any significance in your diagnosis?

A No.

Q Do they play any significance in your opinion concerning causation?

A No.

Q In your view could they be significant in any way whatsoever?

A No.

Q I think you also indicated that the scarring that you saw in the tissue was desmoplastic?

A Yes.

Q It was all desmoplastic?

A That was my interpretation of it.

Q That's your interpretation, although it is difficult at times through a light microscope to distinguish between mature and desmoplastic scarring?

A Yes.

Q Can a bronchogenic carcinoma which arises approximate to a scar, to a mature scar?

A Proximal?

Q Proximal, around, near?

A Okay, you mean "proximate".

Q Sorry.

A I mean, when you use the term "proximal", I would think farther up the trachial bronchiole tree. You mean "adjacent to".

Q I will use a different term. Can a bronchogenic carcinoma that appears adjacent to, near, in close proximity with a mature scar, be desmoplastic?

A Yes.

Q I'm sorry. I'm looking at my notes to find out what else I'd like to cover.

Q Can a cancer that is due to a scar, speaking, of course, still of bronchogenic carcinoma, can a cancer due to a scar, a mature scar also be desmoplastic?

MS. WALTERS: Do you mean a cancer caused by the scar?

MR. ALLINDER: Arising from.

A I don't think that happens.

Q That is not a possible --

A Well, I think --

Q Situation?

A Well, I think I discussed this with Mr. Young. The scar is there. I can't conceive of how collagen, deposited collagen can cause a cancer. So, you know, I'm not following your question. I think I answered Mr. Young to the effect that why I don't think it's due to the scar, the scar is sort of a result rather than a cause.

Q Going back to my questions regarding the doubling time and the time between subclinical, preclinical, clinical, is it altogether impossible to determine when a neoplasm occurs?

A It depends on how precise you want to be. I

think it's impossible to give a date. I think it's possible to give a range, but I think it's not possible to give a date.

Q In this particular case you have given us a range already of two to fifteen or two to twenty years, whatever that was. Is it possible to be more precise than that?

A Not for me.

Q And I am assuming that you're saying that it is not possible to a reasonable degree of medical probability?

A Yes.

Q To give that opinion?

A Yes.

Q Do you think that it is possible for anyone within the scientific community to the same standard to give that sort of opinion?

A No.

Q It is not impossible?

A I'm sorry. I think it is not possible for anyone to do that unless they have considerably more information than is available to me.

Q Your opinion concerning the causation, as I understand it, depends upon two principal factors: your diagnosis of poorly differentiated adenocarcinoma and

the history of smoking, is that correct?

A Yes.

Q And it is your opinion that adenocarcinoma, or at least the poorly differentiated subtype that we have in this case, does not occur in non-smokers?

A It is my opinion that it is more likely than not that it occurred as a result of smoking.

Q That wasn't my question though. I asked, my question was, is it your opinion that poorly differentiated adenocarcinoma does not occur in non-smokers?

A That is not my opinion that it does not occur in non-smokers.

Q Do you think that, or do you agree there has been an increased incidence of adenocarcinoma in the United States?

A I think there are many indications that there is an increase in the total numbers of adenocarcinoma and also in the relative incidence of adenocarcinoma.

Q Is there a difference in the incidence of adenocarcinoma between men and woman?

A Historically there has been. I'm not sure that there is at the present time. Historically woman develop more adenocarcinomas and men develop more squamous cell carcinoma but as the data indicate,

adenocarcinomas are increasing in numbers and relatively in frequency at the expense of squamous cell carcinoma, so that I'm not sure that I have seen a study that would give a direct comparison between men and woman with relative incidence of adenocarcinoma. I think the latest figures that I saw, I think, still showed that men got more lung cancers in general, although the woman were increasing at a much more rapid rate than were the men.

Q Do you think the increased incidence of adenocarcinoma is real?

A I think that as far as I can tell it is real.

Q Does the increased incidence of adenocarcinoma suggest the possibility that there are changing risk factors for that disease?

A It certainly rings a bell that would set everyone in search of that possibility, but I think that, I certainly have responded to the difference by wondering if there is a differences in the etiology, but I'm not sure that I have seen anything that would confirm that a difference in etiology has occurred.

Q Does the, can the clinical course for adenocarcinomas vary between individuals?

A Yes.

Q Are all adenocarcinomas desmoplastic?

A Not all of them, but nearly all of them.

Q I think rather than sitting in front of you and review my notes, I would just as soon take about a five minute break and reconvene, if that's okay with you.

MR. ALLINDER: What time do you have, Cindy?

MS. WALTERS: 5:25.

MR. ALLINDER: I don't think I will have much more, so it appears we'll be done before the end of the day. And I will try not to take more than five or ten minutes to review my notes. Thank you.

(A short recess was taken.)

THE WITNESS: Just for my own purposes, because I'm the only non-lawyer here, except for you, I understand I'm under subpoena to be here tomorrow. I'm pleased if we're finished today, but also I'm willing to complete this Subpoena and be here tomorrow.

MR. YOUNG: I've issued the Subpoena. I'm telling you as soon as someone says they're done with all their questions, that you're released from the Subpoena and won't have to show up tomorrow.

THE WITNESS: Thank you.

MR. ALLINDER: And I am, indeed, done with my examination.

MR. YOUNG: So you're released from the Subpoena.

(Whereupon, the deposition concluded at 5:35 p.m.)

SIGNATURE SHEET

I, Darryl Carter, have read the foregoing transcript of the testimony given at the deposition held on January 31, 1991, and it is true and accurate to the best of my knowledge as originally transcribed or with the changes as noted on the attached Errata Sheet.

_____

DARRYL CARTER

STATE OF CONNECTICUT

COUNTY OF _____

Sworn and subscribed to before me this _____day of_____, 1991.

_____

Notary Public

My commission expires _____.

STATE OF CONNECTICUT)
) ss: Bristol, Connecticut
COUNTY OF HARTFORD)

I, Kathleen M. Sweeney, a Notary Public duly commissioned and qualified in and for the county of Hartford, State of Connecticut, do hereby certify that pursuant to notice, there came before me on the 22nd day of August, 1991, at 10:00 a.m., the following named person, to wit: DR. DARRYL CARTER, who was by me duly sworn to testify to the truth and nothing but the truth of his knowledge touching and concerning the matters in controversy in this cause; and that he was thereupon carefully examined upon his oath and his testimony reduced to writing under my direction; that the deposition is a true record of the testimony given by the witness.

I further certify that I am neither attorney nor counsel for, nor related to, nor employed by any of the parties to the action in which this deposition is taken, and further that I am not a relative or employee of any attorney or counsel employed by the parties hereto or financially interested in the action.

I further certify that the original transcript was sent to the witness for reading and signing. Upon its return, the original transcript is to be forwarded to

Attorney Young together with the original exhibits.

In witness whereof I have hereunto set my hand and affixed my notarial seal this 30th day of August, 1991.

Kathleen M. Sweeney
Notary Public

My commission expires
3/31/92

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CARTER EXHIBITS FOR IDENTIFICATION